Alabama Medicaid Agency
Pharmacy and Therapeutics Committee

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Dose Simplification Overview: A Clinical Evaluation
August 11, 2004

I. Introduction

State Medicaid agencies like the Alabama program are charged with providing a clinically sound Preferred Drug List. This task is complicated by the introduction of more brand product formulations, complex outcomes presented in the literature, and direct marketing to healthcare professionals and consumers.

In the past two-to-three years, there has been an influx of products brought to market as either combinations of already available generic medications or as once-daily formulations. These products offer more convenient dosing regimens for patients, but may or may not offer a significant benefit on the clinical endpoint of the disease. For example, a study by Baird, et al. looked at once-daily versus twice-daily metoprolol and found significant improvements in adherence but no differences in urine drug levels or in blood pressure between patients in the two groups.[1]

All future pharmacotherapy reviews will contain relevant evidence-based literature (when available) pertaining to combination agents and once-daily formulations (dose simplification), citing documented clinical benefit/no benefit when compared to the alternative prescription agent. The purpose of this summary is to provide a general overview of the literature, looking at the impact of medication administration frequency on adherence.

II. Evidence

Studies have shown that as frequency increases, medication adherence decreases, with compliance percentages of QD dosing at 87% and QID dosing at 39%.[2] A 1994 report of the Task Force for Compliance found that 29% of patients stopped medication early, 22% of patients took doses differing from the prescribed regimen, 14% of patients did not have their prescription filled, and 13% filled their prescription but did not take any of the medication.[3] The report also found that adherence with prescribed medications decreases over time.

A study published in 2000 looked at patient adherence from 1990 to 1998, integrating 30 medication adherence studies.[3] Highlights from the analysis that pertain to dosing simplification are listed below. Other studies focused on patient confidence in the provider, knowledge about medications, psychosocial factors, medication errors, and other compliance interventions.

- Eisen, et al. showed once-daily adherence (as measured by electric pill count) was 96%, twice-daily was 93%, and three-times daily was 83.8%.
- Kruse, et al, found a mean adherence rate of 75.7% in their study, with an adherence rate of 67% in those taking medications four-times daily and 85% with twice-daily. The study did not evaluate a once-daily dosing regimen.[4]
- Balestra, et al. reported in HIV populations, adherence was 56.5% and a clear decrease in adherence was documented with advanced disease and multiple medications.
- Kruse, et al. reported an adherence rate with antihypertensive medications of 88% with once-daily medication, and 87.9% with twice-daily treatment. There was no difference in the once-daily versus twice-daily dosing schedules.
- Richardson, et al. discovered an association with greater noncompliance in those under age 66 and with longer treatment.
- Four out of seven studies found that with increased complexity of the dosing regimen, adherence rates decreased.

- In a study of 4,900 patients in a rural area, greater adherence was observed in individuals less than fifteen and greater than seventy years of age.[5] Overall, of 20,921 prescriptions written, 1,072 were not redeemed. The non-redemption rate was highest for prescriptions issued on weekends and for prescriptions issued by trainee general practitioners. The study did not report statistical significance.
- A patient's confidence in their provider consistently had a positive influence on their willingness to comply with medical treatment.
- Adherence studies also showed there were more 24 -hour periods without any medications with once-daily regimens as compared to twice-daily regimens.

In one study reported by Bartels and published in the Archives of Internal Medicine, dose simplification improved adherence from 59% with a TID antihypertensive regimen, to 84% with a once-daily regimen.[6, 7] The study did not, however, report adherence rates for BID treatment to a once-daily regimen.

Another study published in 2001 looked at 76 medication adherence studies using electronic monitoring.[8] The mean dose-taking adherence rate was 71% (range, 34%-97%) and declined as the number of daily doses increased: 1 dose = 79%, 2 doses = 69%, 3 doses = 65%, and 4 doses = 51%. Adherence was only significantly greater for a once-daily regimen versus the three-times daily dose (P=0.008), the once-daily versus four-times daily regimen (P<0.001), and the twice-daily versus four-times daily regimens (P=0.001). There were no statistically significant differences between once-daily and twice-daily regimens or between twice-daily and three-times daily regimens.

Multiple studies have evaluated medication adherence. ***However, there is limited evidence relating to improved clinical endpoints with increased adherence; additional studies are needed to further clarify the benefits of dose simplification. Any such clinical information on disease specific endpoints will be included in each pharmacotherapy review.***

III. Conclusion

In the analysis integrating 30 medication adherence studies, six studies evaluated compliance between once-daily and twice-daily dosing. Two out of the six studies found that compliance did not differ between once-daily and twice-daily regimens.[3] However, adherence did decrease with an increased number of doses. The analysis also reviewed seven studies looking at the impact of the complexity of a dosing regimen on adherence. Four out of the seven studies found that increased complexity decreased adherence rates. Finally, it was found that there were more 24-hour periods without any medications with once-daily regimens. Therefore, a twice-daily dose schedule may circumvent the occurrence of numerous days without any medication.

In general, studies have shown the greatest benefit on adherence from dose simplification may be from moving QID regimens to QD or BID dosing regimens, or in moving TID regimens to QD dosing.[3, 8] Studies that have evaluated twice-daily to three-times daily regimens and once-daily to twice daily regimens have not shown as great of an impact on adherence.

Current evidence suggests that many medication interventions (simplification of dose and frequency) result in increased adherence, but not all of them lead to improvement in treatment endpoints. Decreasing the dose frequency may offer benefits; however, studies indicate not all patients, medications, or diseases may be candidates for regimen simplification. Most importantly, increased adherence has not been shown to have a positive impact on the clinical endpoint in all cases.[1, 3] Available disease specific adherence evidence should be considered in every pharmacotherapy review, with decisions and recommendations based upon established improvement in clinical endpoints.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antidiabetic Agents
August 11, 2004

I. Overview

Diabetes mellitus is a metabolic disorder characterized by high blood sugar levels. The disorder can be classified as either type 1 (insulin dependent) or type 2 (non-insulin dependent) diabetes. Other less common forms of diabetes are gestational diabetes, drug-induced diabetes, and immune-mediated diabetes. Diagnosis today is based on pathogenesis and clinical presentation rather than age of onset. Ninety percent of diabetics have type 2 disease, which can be reflective of physical inactivity and other lifestyle characteristics.[1] In type 2 diabetes, although endogenous insulin is present, plasma insulin concentrations may be decreased, increased or normal. Glucose-stimulated secretion of endogenous insulin is frequently reduced, and decreased peripheral sensitivity to insulin is almost always associated with glucose intolerance. In comparison, type 1 diabetes results from autoimmune destruction of the pancreatic β-cell, responding to insulin replacement therapy to restore deficient levels of endogenous insulin and temporarily restore the ability of the body to properly utilize carbohydrates, fats, and proteins. Obesity may be a confounder as overlapping insulin resistance with β-cell dysfunction may result in diabetes.

Nearly 16 million Americans (7% of the population) have diabetes and there is likely one person undiagnosed for every two persons currently diagnosed with the disease.[1] In 2002, antidiabetic medications accounted for 208 prescriptions per 1000 national Medicaid members.[2] Uncontrolled diabetes results in microvascular, macrovascular and neuropathic complications. This disease is the leading cause of blindness in adults and is the leading contributor to the development of end-stage renal disease. Additional metabolic abnormalities commonly seen in diabetic patients include obesity, hypertension, hyperlipidemia, and impaired fibrinolysis. Epidemiologic data indicate that the incidence of obesity in children with type 2 diabetes is increasing such that 8-45% of children with newly diagnosed diabetes have nonimmune-mediated diabetes mellitus.[2]

Although type 1 diabetes is likely initiated by the exposure of a genetically susceptible individual to an environmental agent, type 2 diabetes is a heterogenous disorder with multiple risk factors.[3] Risk factors for the development of type 2 diabetes include:

- Family history (parents or siblings with diabetes)
- Obesity (>20% over ideal body weight or BMI $\geq$27kg/m^2)
- Habitual physical inactivity
- Prevalence increases with age and in women; and in some groups of Native Americans, Hispanic Americans, Asian Americans, African American and Pacific Islanders
- Previously identified impaired glucose tolerance or impaired fasting glucose
- Hypertension ($\geq$ 140/90mmHg)
- HDL cholesterol $\leq$ 35mg/dL and/or a triglyceride level $\geq$ 250mg/dL
- History of gestational diabetes or delivery of a baby >9 pounds
- Polycystic ovary disease

Proper treatment, both pharmacological and non-pharmacological with lifestyle modifications, can reduce cardiovascular mortality, mortality from other diabetic complications, and help diabetic patients live healthier, longer lives.

II. Evidence Based Medicine and Current Treatment Guidelines

United Kingdom Prospective Diabetes Study (UKPDS)

The UKPDS diabetes initiative, started in 1977, was a multi-center, randomized, controlled intervention trial, comparing treatment with conventional diet-based blood glucose control therapy or intensive pharmacotherapy with a sulfonylurea, insulin, or metformin. The primary goal of the study was to determine if glycemic control in type 2 diabetes prevents diabetic complications and their associated morbidity and mortality. The study included various subsets, looking at blood pressure control and efficacy of combination pharmacotherapy treatments. Results from the trial were published in 1998 and involved 3,867 newly diagnosed type 2 diabetic patients.[4] The study provided definitive evidence for the benefit of intensive management of blood glucose level and blood pressure in patients with type 2 diabetes.[5]

The legacy of this study continues, five years after completion of the study. In fact, post-study monitoring is continuing to determine if findings from UKPDS have influenced usual care, if vascular benefits of intensive therapy have been sustained, and if the status of borderline or unexpected results might change with longer observation. Full results of the five-year post-study monitoring period are expected in 2004; however, preliminary data was reported at the International Diabetes Federation Scientific Meeting in Paris, in the fall of 2003. Highlights of the report include:

- Only a quarter of patients had achieved the target HbA1c level of <7.0% by the end of post-study monitoring, even though most were receiving insulin treatment at the time.
- Participation in the intensive blood glucose lowering group was associated with a significantly lower rate of any diabetes-related endpoint (e.g. myocardial infarction, stroke, renal failure, retinopathy, death from hyper or hypoglycemia) and of microvascular complications.[6]
- Intensive therapy during the study period was associated with a lower risk of diabetes-related death during post-study monitoring.
- The benefit of intensive therapy on fatal or non-fatal myocardial infarction, borderline in the study, was still weak by the end of post-study monitoring, but had become statistically significant.
- Despite a doubling of the percentage of patients taking three or more antihypertensive medications during the post-study period, only one in six patients had achieved a systolic blood pressure of <130mmHg and a diastolic blood pressure of <80mmHg at the end of this time.
- Metformin therapy in overweight patients substantially reduced the risk of any diabetes-related endpoint, all-cause mortality, diabetes-related deaths and myocardial infarction compared with conventional therapy. These risk reductions remained significant during the post-study period.[7]
- There were unexpected increases in all-cause mortality and diabetes-related deaths in patients taking combination sulfonylurea plus metformin compared with sulfonylurea monotherapy in UKPDS. These differences were no longer evident at the end of post-study monitoring.
- By the end of the post-study monitoring period, the relative risk reductions for any diabetes-related endpoint, diabetes-related deaths, and stroke, were no longer statistically significant. However, for microvascular disease, a significant but attenuated risk reduction remained in the group with tight blood pressure control.[8]

Subset studies from UKPDS have published other important data regarding treatment of type 2 diabetic patients. In addition, the Diabetes Control and Complications Trial (DCCT), the "sister" study to UKPDS for type 1 diabetes, also produced support in favor of intensive treatment. Brief descriptions are provided in Table 1.

Table 1. Additional Studies

Study	Sample	Duration	Results
UKPDS 13[9]	n=2,520 type 2 diabetics	3 years	A comparison of the relative efficacy of randomly allocated diet, sulfonylurea, insulin, or metformin showed: ▪ Mean fasting glucose concentrations were significantly lower at 3 years in patients allocated to chlorpropamide, glibenclamide, or insulin rather than diet alone (7.0, 7.6, 7.4, and 9.0mmol/l respectively; P<0.001). ▪ Mean body weight increased significantly with chlorpropamide, glibenclamide, and insulin but not diet (by 3.5, 4.8, 4.8, and 1.7kg; P<0.001). ▪ In obese patients, metformin was as effective as the other drugs with no change in mean body weight and significant reduction in mean fasting plasma insulin concentration (P<0.001). ▪ More hypoglycemic episodes occurred with sulfonylurea or insulin than with diet or metformin.
UKPDS 24[10]	n=458 type 2 diabetics, uncontrolled with diet and with hyperglycemic symptoms; 1,620 patients controlled with diet alone and no hyperglycemic symptoms	6 years	In comparing a sulfonylurea, insulin and metformin therapy in patients uncontrolled with diet: ▪ Patients allocated to insulin had lower fasting plasma glucose levels than did patients allocated to oral agents, while HbA1c remained similar. ▪ By year 6, 51% of patients allocated to ultralente insulin required additional short-acting insulin and 66% of patients allocated to a sulfonylurea required additional therapy with metformin or insulin to control symptoms. ▪ Patients in the insulin group gained more weight and had more hypoglycemic attacks than did patients given sulfonylureas.
UKPDS 28[11]	n=591 type 2 diabetics, on maximum doses of sulfonylureas	3 years	In accessing the efficacy of the early addition of metformin in sulfonylurea-treated type 2 diabetics: ▪ Fasting plasma glucose concentrations decreased by a mean –0.47mmol/l in the combination group, compared with an increase of 0.44mmol/l in patients on sulfonylurea alone (P<0.00001). ▪ HbA1c levels were 7.5 and 8.1% for the combination versus sulfonylurea alone group, respectively (P=0.006). ▪ Only 7% of those allocated to metformin plus sulfonylurea developed marked hyperglycemia compared to 36% of those allocated to monotherapy with a sulfonylurea (P<0.0001).
UKPDS 49[12]	n=4,075 type 2 diabetics, age 25-65 years	9 years	In assessing how often diet alone, insulin, sulfonylurea, or metformin can achieve glycemic control targets: ▪ After 9 years of monotherapy with diet, insulin, or sulfonylurea, 8%, 42%, and 24%, respectively, achieved fasting plasma glucose levels less than 7.8mmol/l (140mg/dl) and 9%, 28%, and 24% achieved HbA1c levels below 7%. ▪ Of patients randomized to metformin therapy, 18% attained fasting plasma glucose levels less than 7.8mmol/l and 13% attained HbA1c levels below 7%. ▪ Patients less likely to achieve target levels were younger, more obese, or more hyperglycemic than other patients.
DCCT[13]	n=1,441 patients with type 1 diabetes, age 13-29	6.5 years	Patients were randomized to intensive treatment (3-4 insulin injections or continuous subcutaneous insulin infusion, plus home blood glucose monitoring) or conventional treatment (1-2 insulin injections plus home urine glucose testing and blood glucose testing). In evaluating the effect of hyperglycemia on the microvascular complications of type 1 diabetes: ▪ Intensive treatment reduced the risks of retinopathy, nephropathy, and neuropathy by 35% to 90% compared to conventional treatment. ▪ Absolute risks of retinopathy and nephropathy were proportional to the mean HbA1c over the follow-up period preceding the event. ▪ Intensive treatment was most effective when begun early, before complications were detectable, and the rate of progression of complications remained less for the intensive group. ▪ The benefits of intensive treatment extended well beyond the period of the most intensive implementation.

Treatment Guidelines and Recommendations

American Diabetes Association[14]

1. Diagnosis of diabetes mellitus*:
   - Symptoms of diabetes plus casual plasma glucose concentration ≥200mg/dl (11.1mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss. OR
   - FPG ≥126mg/dl (7.0mmol/l). Fasting is defined as no caloric intake for at least 8h. OR
   - 2-h postload glucose ≥200mg/dl (11.1mmol/l) during an OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.

   *In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day. The third measure (OGTT) is not recommended for routine clinical use.

2. Introduction of pre-diabetes as defined by the following diagnosis criteria. Patients with impaired fasting glucose and/or impaired glucose tolerance are referred to as having "pre-diabetes", indicating high risk for the development of diabetes.
   Fasting plasma glucose
   <100mg/dl = normal fasting glucose
   100-125mg/dl = impaired fasting glucose
   ≥ 126mg/dl = provisional diagnosis of diabetes, with confirmation

   Oral glucose tolerance test
   2-h postload glucose <140mg/dl = normal glucose tolerance
   2-h postload glucose 140-199mg/dl = impaired glucose tolerance
   2-h postload glucose ≥ 200mg/dl = provisional diagnosis of diabetes, with confirmation

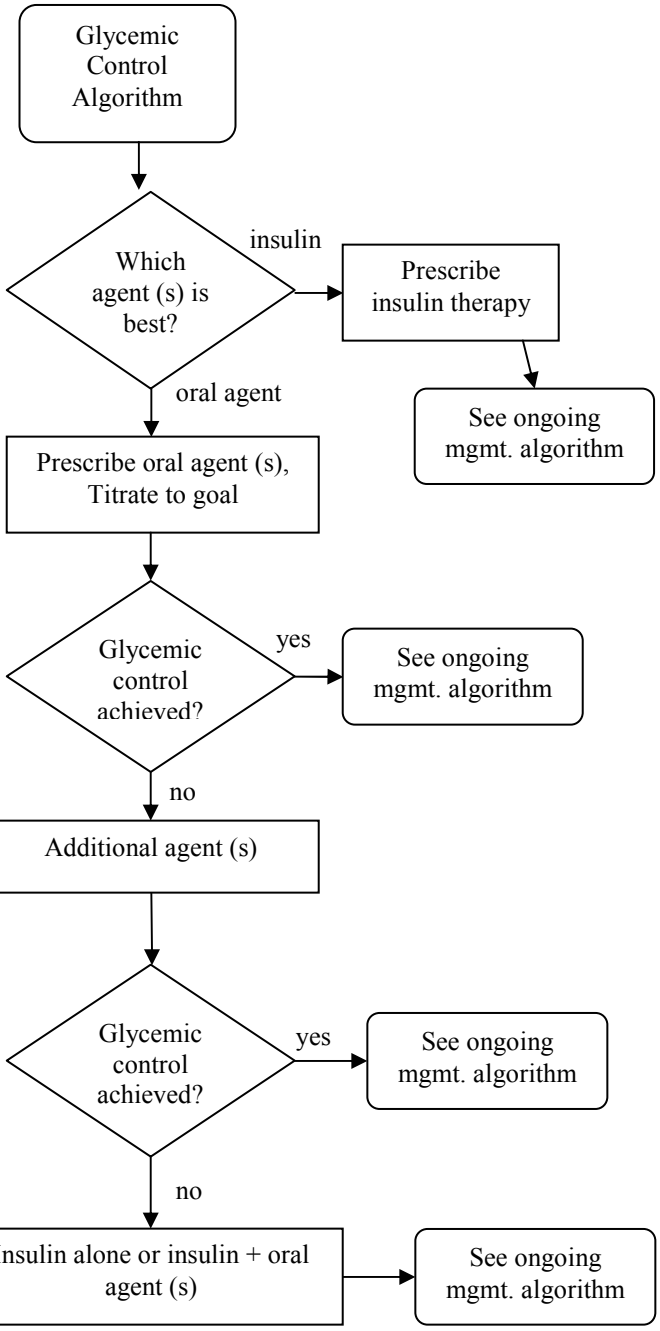
3. Standards of care as revised in the 2004 Clinical Practice Recommendations:
   - HgA1c: <7.0% (nondiabetic range is 4-6%), however, more stringent goals can be considered in individual patients based on epidemiological analyses suggesting there is no lower limit of HgA1c at which further lowering does not reduce the risk of complications. However, this may increase the risk of hypoglycemia in those patients.
   - Preprandial plasma glucose: 90-130mg/dl
   - Postprandial plasma glucose: <180mg/dl
   - Blood pressure: <130/80mmHg (based on ALLHAT), treatment with an ACEI or ARB is recommended
   - LDL cholesterol: <100mg/dl
   - Triglycerides: <150mg/dl
   - HDL: >40mg/dl
   - Total cholesterol: Diabetic patients over age 40, with a level of ≥135mg/dl, should receive statin therapy to achieve an LDL reduction of approximately 30%, regardless of baseline LDL levels.
   - Anti-platelet: Aspirin therapy is recommended as primary and secondary therapy at a dose of 75-162mg/day. Plavix can be considered in aspirin-intolerant patients.
4. Pharmacological Treatment
   Diagnosis→Therapeutic lifestyle changes→Monotherapy with oral agents→Combination therapy with oral agents→Combination therapy with oral plus insulin therapy.

The American Association of Clinical Endocrinologists (AACE)[15]
1. A multidisciplinary approach to the treatment of diabetes should include a health-care team consisting of a clinical endocrinologist, diabetes-trained nurse, certified diabetes educator, pharmacist, psychologist and an exercise physiologist. 2. Intensive therapy should be initiated for both type 1 and type 2 diabetics. Intensive therapy is defined as a comprehensive program of diabetes care that includes, as two of its components, frequent self-monitoring of blood glucose levels and more complex and sophisticated regimens for maintaining near-normal glucose levels. 3. Type 1: Intensive treatment for type 1 diabetics likely includes multiple insulin injections daily or subcutaneous insulin infusion therapy. 4. Type 2: Intensive treatment for type 2 diabetics should not be based on trial-and-error. The cornerstone for type 2 diabetes treatment is proper diet, exercise and education. Once a nutrition and exercise program have been initiated, oral medications can be given if needed. Choices for initial oral agents should be based on desired outcome, individual response, and side effect profiles. The clinical endocrinologist should lead the team in clinical judgments pertaining to the best combinations of medications for each individual patient. 5. Proper treatment of comorbid conditions is critically important for achieving optimal outcomes in patients with diabetes mellitus. 6. The AACE guidelines stress tighter control of blood glucose in both type 1 and type 2 diabetics for significant reductions in the development and progression of microvascular complications (per DCCT and UKPDS). 7. Finally, AACE recommends management of diabetes mellitus through a patient-physician contract, defining both the patient and physician responsibilities.

Institute for Clinical Systems Improvement[16]
1. Clinical highlights: • Focus on cardiovascular risk reduction (blood pressure, lipids, ASA, and tobacco cessation). ACE inhibitors and ARBs are preferred first-line agents; however, combination therapy should include thiazide diuretics. • Glycemic control of less than 7% often required frequent drug intensification and use of combination therapy. See glycemic control algorithm on page 6. • Aggressive blood pressure control is just as important as glycemic control. Systolic blood pressure level should be the major factor for detection, evaluation, and treatment of hypertension. This may require the use of two or more agents (to include thiazide diuretics). • Self-management support (includes nutrition therapy, physical therapy, education for self management, foot care and community resources) is necessary for people with diabetes to manage their disease. • Prevent microvascular complications through annual eye exams, foot risk assessments and foot care counseling, and annual screening for proteinuria. 2. Treatment Goals for individuals: • HbA1c: <7% • Blood pressure control: <130/80mmHg • Lipid levels: LDL<100mg/dl • ASA / antiplatelet medication unless contraindicated • Tobacco cessation if indicated 3. Maintain Treatment Goals: Monitor HbA1c every 3-6 months — Monitor lipid profile yearly Monitor blood pressure at each visit — Stress proper nutrition and exercise 4. Annual Assessment of complications: Targeted history and physical exam — Specialist dilated eye exam Renal assessment — Comprehensive foot exam Cardiovascular and cerebrovascular complication assessment Special considerations

Institute for Clinical Systems Improvement cont'd[16]

Glycemic Control Algorithm



Information for ongoing management algorithms is available at www.icsi.org.

Table 2. General Adherence Evidence in Diabetes Mellitus

Study	Sample	Duration	Results
Predictors of medication adherence in type 2 diabetes[17]	n=775	1-5 year longitudinal cohort study of older adults	In evaluating the relationship between self-reported health status data, subsequent antidiabetic medication adherence, and healthcare service utilization in type 2 diabetics in a managed care setting: • Increased comorbidity severity and an emergency room visit during the year prior to enrollment in a Medicare HMO were independently associated with decreased antidiabetic medication possession rations after enrollment. • Increased antidiabetic medication possession ratios remained the strongest predictor of decreased healthcare utilization (8.6% to 28.9% decrease in annual healthcare utilization with every 10% increase in medication possession ratio; $p<0.001$). • Summary: This study found a strong association between decreased antidiabetic medication adherence and increased healthcare service utilization in this population.
Polypharmacy and medication adherence in patients with type 2 diabetes[18]	n=128	-	In evaluating medication adherence and predictors of suboptimal adherence in a community cohort of patients with diabetes and to test the hypothesis that adherence decreases with an increased number of prescribed medicines: • Patients were taking an average of 4.1 (± 1.9) diabetes-related medications. The average day adherence was 6.7 ± 1.1 days. • Total number of medications prescribed was not correlated with medication adherence. • Adherence was significantly lower for medicines not felt to be improving current or future health ($p<0.001$). • Among patients with 3 or more medicines, 71% with suboptimal adherence were perfectly adherent with all but 1 medicine. • Side effects were the most commonly reported problem with medication use. • Of 29 medicines causing side effects that interfered with adherence, 24 (83%) did so for >1 month, and only 7 (24%) were reported to the patient's primary care physician. • Summary: In this sample, patients reported very high medication adherence rates regardless of the number of medicines prescribed.
Utilization associated with pharmaceutical adherence in a diabetic population[19]	n=57,687	Retrospective cohort design using insurance claims in an open access, nonmanaged care setting	To determine whether adherence to pharmaceutical therapy affects well-being and total utilization of medical care with diabetes. Results showed: • A threshold effect was observed, where a target level of adherence was needed before overall medical outcomes were impacted. • Increased pharmaceutical adherence was associated with fewer emergency room visits and inpatient admissions. • Increased medication adherence was not associated with decreased **overall** healthcare utilization (pharmacy and medical) because medication resources offset medical care differences. • Summary: Increased adherence with medications was associated with decreased use of medical care services, suggesting improved disease control and well-being.
Adherence to oral therapy for type 2	-	Literature Review	In order to evaluate the various patient-related, disease-related, and demographic variables affecting medication adherence, a literature

diabetes: Opportunities for enhancing glycemic control[20]			search of all scientific literature, clinical practice guidelines, and internet sources was performed: • Among 85,888 diabetic patients with new prescriptions for antidiabetic medications, the average compliance rate of 79% was observed. • Persistence varied with different agents and ranged from 31% for alpha-glucosidase inhibitors to 60% for metformin. • Another study showed that age and show rate for office appointments is highly correlated with glycemic control. • One study looked at compliance rates with a sulfonylurea alone, metformin alone, and a combination of both drugs. Results: The percentage of acceptable adherence (>90%) was similar for patients receiving treatment with one of the single agents, while only 13% of patients receiving combination therapy were treatment-adherent. • Once daily dosing and/or fewer total tablets taken per day were strongly associated with better adherence rates; each increase in daily dosing frequency corresponded with a 22% decrease in adherence. • Another Medicaid population study by Daily, Kin, and Lian showed that simple, single-drug regimens (monotherapy) were associated with better adherence and persistence than more complex, multidrug regimens.

α - Glucosidase Inhibitors (AHFS 682002) Single Entity Agents

I. Comparative Indications for the α - Glucosidase Inhibitors

The α-Glucosidase Inhibitors are used in the treatment of type 2 diabetes mellitus. They work by delaying carbohydrate breakdown and glucose absorption in the small intestine, and result in a reduction in postprandial hyperglycemia.

Acarbose (Precose) is a complex oligosaccharide produced by fermentation of *Actinoplanes utahensis*. It is a reversible, competitive inhibitor of the α-glucosidase enzymes (e.g. glucoamylase, sucrase, maltase, isomaltase) that hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the intestinal brush-border.[21] In contrast to sulfonylureas, acarbose does not enhance insulin secretion and does not produce hypoglycemia when given as monotherapy. Because the mechanisms of action of acarbose and sulfonylureas are different, the effects of these drugs on glycemic control are additive when used in combination.

The other agent in this class, miglitol (Glyset), has a mechanism of action similar to acarbose. Miglitol works through reversible inhibition of membrane-bound intestinal α-glucosidase hydrolase enzymes in the brush border of the small intestines.[22]

Table 1 lists the agents included in this review. This review encompasses all dosage forms and strengths.

Table 1. α - Glucosidase Inhibitors in this Review

Generic Name*	Formulation	Example Brand Name
Miglitol	Oral	Glyset
Acarbose	Oral	Precose

*There are no generic formulations available for any of the medications in this class.

This class of drugs is contraindicated in patients with diabetic ketoacidosis, cirrhosis, inflammatory bowel disease, colonic ulceration, partial intestinal obstruction, and in patients predisposed to intestinal obstruction.[21, 22] Alpha-glucosidase inhibitors should not be used in patients who have chronic intestinal diseases associated with marked disorders of digestion or absorption and in patients who have conditions that may deteriorate as a result of increased gas formation in the intestine.

Table 2. FDA-Approved Indications for the α - Glucosidase Inhibitors[21, 22]

Brand Name	Monotherapy in Type 2 Diabetes	Combination Therapy with a Sulfonylurea in Type 2 Diabetes	Combination Therapy with metformin or insulin in Type 2 Diabetes
Miglitol	✓ **Adjunct to diet**	✓	-
Acarbose	✓ **Adjunct to diet**	✓	✓

In the treatment of type 2 diabetes, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in treatment of the obese diabetic patient. Treatment with acarbose and miglitol should be viewed as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restrictions.

II. Pharmacokinetic Parameters of the α - Glucosidase Inhibitors

Acarbose
In pharmacokinetic studies, less than 2% of an oral dose of acarbose was absorbed as active drug.[21] Because the drug acts locally in the gastrointestinal tract, low systemic bioavailability is desired.
Acarbose is metabolized exclusively in the gastrointestinal tract, by both intestinal bacteria and digestive enzymes. At least 13 metabolites have been separated from urine specimens, one having alpha-glucosidase inhibitory activity. The small amount of acarbose that is absorbed as intact drug is almost completely excreted by the kidneys. The plasma elimination half-life of acarbose is approximately 2 hours; consequently, the drug does not accumulate when given three times daily.

Miglitol
A dose of 25mg of miglitol is completely absorbed, whereas a dose of 100mg is only 50-70% absorbed.[22] Miglitol is not metabolized in humans or animals, as metabolites have not been detected in plasma, urine, or feces. The protein binding of miglitol is negligible (<4.0%) and the drug is renally excreted unchanged. The elimination half-life of the drug is approximately 2 hours.

Table 3 compares the pharmacokinetic profiles of miglitol and acarbose.

Table 3. Pharmacokinetic Parameters of the α - Glucosidase Inhibitors[43]

Agents	t_{max} (hr)	Protein Binding (%)	Volume of Distribution	Metabolism	Excretion (%)
Miglitol	2-3	<4.0	0.18L/kg	Drug is not metabolized	Renal (95)
Acarbose	1	N/A	N/A	Exclusively in the GI tract and by digestive enzymes	Feces (51) Renal (<2)

N/A Data is not available in the literature.

III. Drug Interactions of the α - Glucosidase Inhibitors

Digestive enzymes should not be given with this class of medications as they can reduce the effect of acarbose and miglitol.

Studies with acarbose have shown no effect on the pharmacokinetics or pharmacodynamics of nifedipine, propranolol, or ranitidine.[21] Another study showed acarbose did not interfere with the absorption or disposition of glyburide when given in combination.

Miglitol has been studied in combination with several other drugs for possible drug interactions.[22] No effect of miglitol was observed on the pharmacokinetics or pharmacodynamics of either warfarin or nifedipine. However, miglitol may significantly reduce the bioavailability of ranitidine and propranolol by 60% and 40%, respectively.

Table 4 describes other documented interactions with miglitol and acarbose. Level 1 interactions are considered most severe and life threatening, while level 5 interactions are least significant. Some of the documented interactions with miglitol have not been assigned significance ratings.

Table 4. Documented Drug Interactions for Acarbose[23, 24]

Significance	Interaction	Mechanism
2 Delayed, Moderate, Probable	Acarbose and digoxin	Impaired absorption of digoxin, resulting in lower serum digoxin concentrations and decreased therapeutic effects. Digoxin levels should be monitored and adjusted. Giving acarbose 6 hours after digoxin may circumvent this interaction.
-	Miglitol and digoxin	Coadministration may reduce the average plasma concentrations of digoxin by 19% to 28%. In one study, plasma digoxin concentrations were not altered when coadministered with miglitol 100mg TID for 14 days.
4 Delayed, Moderate, Possible	Acarbose and warfarin	Mechanism is unknown. The anticoagulant effect of warfarin may be increased. Anticoagulant function should be monitored and dosage adjustments made as needed.
5 Minor, Possible	Acarbose and metformin	Acarbose may delay the intestinal absorption of metformin. The onset of the effects of metformin may be delayed, however, no special precautions are needed.
-	Miglitol and metformin	Mean AUC and C_{max} values for metformin were 12-13% lower when the volunteers were given miglitol as compared to placebo, but this difference was not statistically significant.
-	Miglitol and glyburide	Decreased AUC and C_{max} values for glyburide occurred when coadministered with miglitol. These differences were not statistically significant.

- = Significance of the interaction has not been established.

IV. Adverse Drug Events

Gastrointestinal effects are the most common adverse reactions reported with this class of medications. In a one-year safety study of acarbose, where patients kept diaries of gastrointestinal symptoms, abdominal pain and diarrhea tended to return to pretreatment levels over time, and the frequency and intensity of flatulence tended to abate with time. This pattern of diminished gastrointestinal symptoms occurs similarly with miglitol. Increased gastrointestinal symptoms seen with acarbose and miglitol are a manifestation of the drugs' mechanism of action and are related to the presence of undigested carbohydrate in the lower GI tract. Rarely, these symptoms may be severe and might be confused with paralytic ileus. Acarbose, in doses exceeding 150mg QD, may be associated with elevated serum aminotransferase (ALT and AST) concentrations. This has not been seen with miglitol. Levels should be monitored every 3 months during the first year of therapy.[24]

Table 5. Gastrointestinal Adverse Events (%), Reported for the α - Glucosidase Inhibitors[21, 22]

Adverse Event	Acarbose	Placebo	Miglitol	Placebo
Gastrointestinal				
Abdominal Pain	19%	9%	11.7%	4.7%
Diarrhea	31%	12%	28.7%	10%
Flatulence	74%	29%	41.5%	12%

V. Dosing and Administration for the α - Glucosidase Inhibitors

The goal of treatment with acarbose should be to reduce both postprandial blood glucose and HbA1c values to normal or near normal using the lowest effective dose, either as monotherapy, or in combination with a sulfonylurea, insulin, or metformin. (miglitol is only indicated for combination use with sulfonylureas) Dosages should be individualized, based on patient response and tolerance. Gradual titration of dose can help reduce GI adverse effects. Titration at 4-8 week intervals is recommended. For miglitol, the usual maintenance dose is 50mg TID. For acarbose, use of the 50mg TID dose may be associated with fewer adverse effects, with efficacy similar to the 100mg TID dose.[21] Table 6 lists the dosing recommendations for the drugs in this class.

Table 6. Dosing for the α - Glucosidase Inhibitors[21, 22, 24]

	Availability	Dose /Frequency/Duration
Miglitol (Glyset)	25, 50 and 100mg oral tablets	Initial: 25mg TID (given at the start of each meal) Maximum dose: 100mg TID (given at the start of each meal)
Acarbose (Precose)	25, 50, and 100mg oral tablets	Initial: 25mg TID (given at the start of each meal) Maximum dose: 50mg TID (for patients 60kg or less) 100mg TID (for patients >60kg)

Special Dosing Considerations

Renal Impairment:

- Due to local action, miglitol dosage adjustment in renal impairment is not feasible. Little information is available on use of miglitol in patients with a creatinine clearance of <25mL/min.
- Long-term studies with acarbose in diabetic patients with a serum creatinine >2.0mg/dl are not available, therefore, treatment in these patients is not recommended.

Hepatic Impairment:

- No influence on hepatic function is expected with miglitol.
- Acarbose is contraindicated in patients with cirrhosis, however, the manufacturer does not make a specific recommendation regarding use of the drug in other hepatic conditions.

Other:

- Safety and efficacy of miglitol in pediatric patients has not been established.
- Safety and efficacy of acarbose in pediatric patients has not been established.
- Both miglitol and acarbose are considered pregnancy category B.

VI. Comparative Effectiveness of the α - Glucosidase Inhibitors

To date, there have been no head-to-head trials comparing miglitol and acarbose. The efficacy for each drug has been established through monotherapy studies and combination trials with other antidiabetic treatments.

Table 7. Additional Outcomes Evidence for the α - Glucosidase Inhibitors

Study	Sample	Duration	Results
STOP-NIDDM: Acarbose vs. placebo on cardiovascular events[25]	n=1,368	3.3 year international, multicenter double-blind, placebo-controlled trial	In evaluating the effect of decreasing postprandial hyperglycemia with acarbose on the risk of cardiovascular disease and hypertension in patients with impaired glucose intolerance: • 341 patients (24%) discontinued participation prematurely; 211 in the acarbose group and 130 in the placebo group. The most common reason was GI adverse effects. • Decreasing postprandial hyperglycemia with acarbose was associated with a 49% reduction in the development of cardiovascular events (hazard ratio 0.51;95% confidence interval;P=0.03) and a 2.5% absolute risk reduction. • Risk reduction was in the risk of myocardial infarction (hazard ratio 0.09;95% confidence interval; P=0.02). • Acarbose was also associated with a 34% relative risk reduction in the incidence of new cases of hypertension (P=0.006) and a 5.3% absolute risk reduction. • Even after adjusting for major risk factors, the reduction in the risk of cardiovascular events and hypertension associated with acarbose treatment was statistically significant. • **Conclusion:** Treating impaired glucose tolerance with acarbose is associated with a significant reduction in the risk of cardiovascular disease and hypertension.
Miglitol plus metformin[26]	n=324	36 weeks	In comparing the efficacy and safety of placebo, miglitol alone, metformin alone, and miglitol plus metformin: • A reduction in mean placebo-subtracted HbA1c of –1.78% was observed with miglitol plus metformin, which was significantly different from treatment with metformin alone (P=0.002). • Combination therapy with metformin and miglitol also resulted in better metabolic control than metformin alone for fasting plasma glucose (P=0.0025), 2 hour postprandial plasma glucose area under the curve (P=0.0001), and responder rate (P=0.0014).
Miglitol therapy with sulfonylureas and insulin[27]	n=33	3 months	In reviewing the usefulness of miglitol on blood glucose and lipid control in patients with type 2 diabetes treated insufficiently with sulfonylureas and insulin: • Blood glucose and HbA1c levels decreased 4.8 and 5.8%, respectively. • A decrease in the number of hypoglycemic episodes was observed (39.4% vs. 3% with miglitol). • The dose of sulfonylurea needed by patients was decreased with the addition of miglitol (P<0.05). • Total cholesterol, HDL, and LDL cholesterol levels were not modified, but there was a reduction in the level of triglycerides (P<0.05). • 15% of patients experienced side-effects, mostly gastrointestinal, that disappeared 2-3 weeks after beginning the treatment.
Acarbose versus metformin as an adjuvant to sulfonylurea[28]	n=18 type 2 diabetics	8 weeks	In a comparison of the effects of acarbose or metformin used as an adjunct with a sulfonylurea in patients with type 2 diabetes not controlled with sulfonylurea monotherapy: • Mean fasting and 2 hour postprandial glucose levels were reduced moderately at the end of 8 weeks in both combination groups (P<0.05). • The 2 hour postprandial blood glucose levels in the group using acarbose plus a sulfonylurea was lower than the level achieved by

			the group using metformin plus a sulfonylurea (P<0.05). • The difference between pre and post treatment levels of the 2 hour postprandial blood glucose level in both arms of the study were statistically significant (delta-acarbose, 5.3 +/- 0.4 vs. delta metformin, 2.9 +/- 0.3, P<0.05). • Drug associated side-effects were observed in 12 patients on acarbose and 3 patients on metformin.
Acarbose delays onset of type 2 diabetes[29]	n=1,368	3.3 year, subset study from the STOP-NIDDM Trial	Patients who develop type 2 diabetes initially pass through a state of impaired glucose tolerance. Investigators looked at whether use of therapies that reduce resistance to insulin or protect beta-cells could prevent or delay the progression of diabetes: • Patients treated with acarbose were less likely to develop type 2 diabetes after 3.3 years of treatment, compared to placebo (17% vs. 26%, P=0.0003). • When acarbose was stopped at the end of the study period, more patients treated with acarbose developed diabetes in the next 3 months than did patients who were treated with placebo (15% vs. 11%).
Efficacy and tolerability of acarbose in Asian patients[30]	n=69 patients with type 2 diabetes	24 weeks	In investigating the efficacy, tolerability, and safety of acarbose in Asian patients inadequately controlled by diet and sulfonylureas: • Acarbose treatment was associated with significantly greater reductions in HbA1c (-0.91% vs. placebo 0.13%, P=0.0018) and 1 hour postprandial blood glucose levels (-2.84mmol/l vs. placebo -0.28mmol/l, P=0.002). • There were no significant differences between the treatment groups regarding changes in fasting blood glucose, fasting 1 hour postprandial serum insulin, urinary glucose, or body weight. • Adverse events occurred with similar frequency in both treatment arms except for drug-related gastrointestinal side-effects with acarbose (acarbose 48.5% and placebo 12.5%).
Acarbose versus tolbutamide for first treatment[31]	n=96 newly diagnosed type 2 diabetics	3 years	When comparing tolbutamide and acarbose with respect to the effect on mean HbA1c: • The difference in mean HbA1c was 0.6% in favor of tolbutamide (90% CI 0.3, 0.9;95% CI 0.2, 1.0). • The difference in mean decrease of fasting blood glucose was 1.0mmol/l in favor of tolbutamide (95% CI 0.3, 1.7). • There were no significant differences in post-load blood glucose, fasting and post-load insulin levels, or lipids. • Significantly more patients in the acarbose group (15 vs. 3) discontinued therapy because of adverse effects, mostly GI.
Acarbose versus glimepiride in type 2 diabetes[32]	n=219 type 2 diabetics uncon-trolled with diet alone	20 weeks	In a comparison of acarbose and glimepiride, looking at the efficacy of, and compliance with either treatment: • Glimepiride was associated with a significantly greater responder rate than acarbose (61 vs. 34%, P<0.001), significantly greater decreases in HbA1c (2.5 +/- 2.2% vs. 1.8 +/- 2.2%, p=0.014), and fasting blood glucose levels (2.6 +/- 2.6mmol/l vs. 1.4 +/-2.8mmol/l, p=0.004), a decreased glucose response to breakfast compared with acarbose (P=0.0001), and was accompanied by significantly greater compliance (P=0.0001).
The PROTECT Study[33]	n=6,142 patients with type 2 diabetes	28 weeks	In a study to access the effectiveness, tolerability and safety of acarbose in patients inadequately controlled with diet alone or with diet plus a sulfonylurea: • HbA1c declined throughout the study for a mean change of –0.66%. • The mean change from baseline in mean postprandial glucose levels was –41mg/dL. • Patients who had been diagnosed with diabetes for less than 1 year and patients who were untreated at study entry responded particularly well to acarbose

Acarbose effect on HbA1c[21]	n=769	-	Fixed-dose monotherapy studies with acarbose produced the following effects on HbA1c: Dose — Change in HbA1c 25mg TID — -0.44 50mg TID — -0.77 100mg TID — -0.74 200mg TID — -0.86 300mg TID — -1.00

Additional Evidence

Dose Simplification: Not Applicable.

Stable Therapy: Since both agents in this class are dosed three times daily, there is no dosing advantage/disadvantage of changing from acarbose to miglitol or from miglitol to acarbose. It has been shown to be beneficial to use acarbose and miglitol as adjuncts to other antidiabetic drug therapy due to differing mechanisms of action. Combination therapy with the alpha-glucosidase inhibitors in patients not adequately controlled with monotherapy may delay initiation or avoid institution of insulin.

Impact on Physician Visits: One study compared glipizide, metformin, and acarbose, looking specifically at use of routine medical care, supplies, medication, adverse events, and treatment failures.[34] Three-year utilization of these services/supplies, etc. ranked the three drugs in the following manner, from least to most services used: glipizide, metformin, and acarbose.

VII. Conclusions

There are multiple therapy options for the treatment of type 2 diabetes. The α - glucosidase inhibitors offer a unique mechanism of action compared to the other oral antidiabetic agents. There are no generic drugs available in this class. The STOP-NIDDM Trial was pivotal in showing clinical benefits in type 2 diabetics treated with acarbose. In addition, these drugs have been shown to offer additive benefits when used in combination with other oral agents, although miglitol has more limited indications than acarbose. One unpublished trial showed equal efficacy between acarbose and miglitol and clinical evidence suggests they are similar in regards to side-effects, dosing frequency, and drug interactions. An advantage to the α - glucosidase inhibitors is they do not produce hypoglycemia, however, due to the mechanism of action, many patients have difficulty tolerating the gastrointestinal side-effects associated with these drugs. Because there are no direct head-to-head studies comparing miglitol and acarbose, one agent cannot be considered clinically advantageous over the other. Therefore, all brand products within the α - glucosidase inhibitor class are comparable to each other and offer no significant clinical advantage over other alternatives in general use.

VIII. Recommendations

No brand α - glucosidase inhibitor is recommended for preferred status.

Biguanides (AHFS 682004) Single Entity Agents

I. Comparative Indications of the Biguanides

The biguanide medications are not chemically or pharmacologically related to other classes of oral antidiabetic drugs. Their mechanism of action is unique to this class. The only product in this class, metformin, works by improving glucose tolerance in type 2 diabetics, lowering both basal and postprandial plasma glucose. Specifically, metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization.[35]

Unlike sulfonylureas, the biguanides do not produce hypoglycemia and they do not cause hyperinsulinemia. During treatment with metformin, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease. Table 1 lists the products covered in this review. Metformin oral solution (Riomet) was not included in this review at the May P&T meeting, but is now eligible for review. Additionally, since the May review, a generic formulation of metformin extended-release 500mg has become available. This review encompasses all dosage forms and strengths.

Table 1. Biguanide Products in this Review

Generic Name	Formulation	Example Brand Name
Metformin	Oral	Glucophage*
Metformin	Oral extended-release	Glucophage XR**
Metformin	Oral Solution	Riomet

*Generic Available.
**Generic Available in 500mg strength only.

The biguanides should not be used in patients with renal disease or renal dysfunction (serum creatinine ≥1.5mg/dl in males and ≥1.4mg/dl in females), congestive heart failure requiring pharmacologic treatment, in patients with known sensitivity to metformin, hepatic disease, or in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis.[33] Metformin should also be temporarily stopped in patients undergoing radiologic studies involving iodinated contrast.

Black Box Warning
Finally, metformin has been associated with lactic acidosis in 0.03 cases per 1000 patient-years. Lactic acidosis can occur due to metformin accumulation during treatment.[35] The risk of developing lactic acidosis is higher in patients with significant renal insufficiency, those with congestive heat failure who are at risk of hypoperfusion and hypoxemia, and the risk increases with age. Risk of lactic acidosis can be minimized with routine monitoring of renal function (especially in the elderly) and with use of the minimum effective dose. Table 2 describes the Food and Drug Administration (FDA) approved indications for the biguanide medications.

Table 2. FDA-Approved Indications for the Biguanides[35]

Brand Name	Monotherapy in type 2 diabetics	Age Specifications	Combination with Insulin or sulfonylurea
Metformin (Glucophage)	✓ Adjunct to diet and exercise	10 years and older	✓ In adults 17 and older
Metformin extended-release (Glucophage XR)	✓ Adjunct to diet and exercise	17 years and older	✓ In adults 17 and older
Metformin oral solution Riomet	✓	10 years and older	✓ In adults 17 and older

II. Pharmacokinetic Parameters

Absorption
The absolute bioavailability of a single metformin 500mg tablet given under fasting conditions is 50-60%.[35] Studies using single oral doses of metformin 500mg to 1500mg, and 850mg to 2550mg, indicate there is a lack of dose proportionality with increasing doses. Food decreases the extent of and slightly delays the absorption of metformin, as shown in studies by a 40% lower mean peak plasma concentration, a 25% lower area under the plasma concentration versus time curve, and a 35 minute prolongation of time to peak plasma concentration, compared to administration during fasting.

The C_{max} of metformin extended-release is achieved with a median value of 7 hours. Peak plasma levels are approximately 20% lower compared to the same dose of metformin, while the extent of absorption is similar. The extent of metformin absorption from metformin extended-release at a 2000mg once daily dose is similar to the same total daily dose administered as metformin 1000mg twice daily.

The rate and extent of absorption (C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$) of metformin oral solution (Riomet) was found to be bioequivalent to that of metformin tablets (Glucophage) under fasting or fed conditions, according to multiple pharmacokinetic studies.[36] No pharmacokinetic data from studies of pediatric patients is currently available. The results of two studies are compared in Table 3.

Table 3. Pharmacokinetic Parameters of a Single 1000mg Dose of Metformin Solution vs. Metformin Tablets[36]

Formulation	C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng.h/ml)	T_{max} (h)
Study 1: Fasting State			
Metformin Solution	1540.1 + 451.1	9069.6 + 2593.6	2.2 + 0.5
Metformin Tablets	1885.1 + 498.5	11100.1 + 2733.1	2.5 + 0.6
T/R Ratio x 100 (90% confidence interval)	81.2 (76.3-86.4)	81.2 (76.9-85.6)	-
Study 2: Fed State			
Metformin Solution	1235.3 + 177.7	8950.1 + 1381.2	4.1 + 0.8
Metformin Tablets	1361 + 298.8	9307.7 + 1839.8	3.7 + 0.8
T/R Ratio x 100 (90% confidence interval)	91.8 (87.4-96.5)	97.0 (92.9-101.2)	-

T-test product (Riomet)
R-reference product (metformin tablets)

A third study has evaluated the effects of a high fat/high calorie meal and a low fat/low calorie meal on the bioavailability of Riomet in comparison with administration in the fasted state. The extent of absorption was increased by 21% and 17% with the low fat/low calorie meal and the high fat/high calorie meal, respectively, compared with the administration in the fasted state. The rate and extent of absorption with high fat/high calorie and low fat/low calorie meals were similar. The mean t_{max} was 2.5 hours under fasting conditions as compared to 3.9 hours with both low fat/low calorie meals and high fat/high calorie meals.

Distribution, Metabolism and Elimination
Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Steady state plasma concentrations of metformin are reached within 24-48 hours. Following oral administration of metformin, about 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma half-life of approximately 17.6 hours. Metformin does not undergo hepatic metabolism or biliary excretion.

III. Drug Interactions of the Biguanides

Drug interactions with the biguanide medications do not differ by formulation (tablet vs. oral solution).

Multiple studies have documented interactions with the biguanide medications. Cationic drugs (amiloride, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim and vancomycin) that are eliminated by renal tubular secretion, theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems.[32] This type of interaction has been documented specifically with cimetidine, where there was a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin area under the curve (AUC). Careful monitoring and dosage adjustments with metformin may be necessary.

Metformin also interacts with certain drugs known to produce hyperglycemia, leading to loss of glycemic control. These drugs include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. Close monitoring is necessary when these drugs are added or removed from treatment protocols of diabetic patients. Table 4 is a description of the clinically significant biguanide drug interactions with ratings of level 1 and 2 (moderate or major, suspected). Other less significant documented interactions with metformin include: acarbose, atropine, belladonna, benztropine, biperiden, dicyclomine, hyoscyamine, oxybutynin, procyclidine and propantheline.

Table 4. Clinically Significant Drug Interactions [23]

Significance	Interaction	Mechanism
1	Metformin and Iodinated Contrast Materials, Parenteral	Iodinated contrast materials-induced renal failure can interfere with the renal elimination of metformin, resulting in increased risk of metformin-induced lactic acidosis. Co-administration is contraindicated; metformin should be temporarily stopped for purposes of the procedure.
2	Metformin and Cimetidine	Cimetidine reduces the renal clearance of metformin by inhibiting renal tubular secretion. Serum concentrations of metformin may be elevated, increasing the pharmacologic effects. Metformin dosage adjustments may be necessary when cimetidine is stopped or started.

IV. Adverse Drug Events Associated with the Biguanides

The biguanides are generally well tolerated. Diarrhea lead to discontinuation of treatment in 6% of patients treated with metformin and 0.6% of patients treated with metformin extended-release.[35] Adverse reactions reported in greater than 5% of metformin patients, and that were more common in metformin than in placebo-treated patients are represented in Tables 5 and 6. In trials of metformin in pediatric patients with type 2 diabetes, adverse reactions were similar to those observed in adults. Adverse drug events for metformin oral solution are similar to those with metformin.

Table 5. Adverse Reactions >5% in a Placebo-Controlled Study of Metformin Monotherapy[35, 36]

Adverse Reaction	Metformin Monotherapy n=141	Placebo n=145
Diarrhea	53.2	11.7
Nausea / Vomiting	25.5	8.3
Flatulence	12.1	5.5
Asthenia	9.2	5.5
Indigestion	7.1	4.1
Abdominal discomfort	6.4	4.8
Headache	5.7	4.8

Table 6. Adverse Reactions >5% in Placebo-Controlled Studies of Metformin Extended-Release[35]

Adverse Reaction	Metformin ER Monotherapy n=781	Placebo n=195
Diarrhea	9.6	2.6
Nausea / Vomiting	6.5	1.5

V. Dosing and Administration of the Biguanides

Dosing with Glucophage, Glucophage XR and Riomet should be individualized on the basis of effectiveness and tolerance, while not exceeding the recommended dose. Glucophage, metformin, and Riomet should be given in divided doses with meals, while Glucophage XR should generally be given once daily with the evening meal. Starting doses should be low, with gradual escalation, both to reduce gastrointestinal side effects and allow the minimum dose required for adequate glycemic control. Dosage titrations should be made in increments of 500mg weekly or 850mg every 2 weeks. A randomized trial showed that patients currently treated with Glucophage, when switched to Glucophage XR once daily, may do this safely at the same total daily dose, not to exceed the maximum (metformin 2550mg per day and metformin XR 2000mg per day).

Table 7. Dosing and Availability of the Biguanide Products[35, 36]

Drug	Availability	Dose /Frequency/Duration
Glucophage	500mg, 850mg, 1000mg tablets	Starting dose: 500mg BID or 850mg QD Maximum daily dose: Adults 2550mg Children 2000mg (age 10-16) Note: Doses >2000mg are better tolerated given TID
Glucophage XR	500mg, 750mg tablets	Starting dose: 500mg QD Maximum daily dose: Adults 2000mg
Metformin	500mg, 850mg, 1000mg tablets generic from Watson, PAR, Mylan	Starting dose: 500mg BID or 850mg QD Maximum daily dose: Adults 2550mg Children 2000mg (age 10-16) Note: Doses>2000mg are better tolerated given TID
Riomet	500mg / 5ml cherry solution	Starting dose: 500mg (5ml) BID or 850mg (8.5ml) QD Maximum daily dose: Adults 2550mg (25.5ml) Children 2000mg (20ml, age 10-16)

Special Dosing Considerations

Renal and Hepatic Impairment:

- Metformin products should not be used in patients with renal disease or dysfunction or in those with hepatic disease.

Other:

- Metformin oral solution (Riomet) can be safely administered per tube (per Ranbaxy Pharmaceuticals).
- Bristol-Myers Squibb reports no studies have been done to evaluate the efficacy of metformin (Glucophage) when crushed and administered, although since the drug is not an extended-release product, they do not anticipate problems.

- Metformin should be used during pregnancy only when clearly indicated. It is a pregnancy category B drug.
- Metformin immediate-release tablets are indicated for use in children age 10 and older and the extended-release tablets are indicated for age 17 and older.
- The metformin oral solution (Riomet) does not contain alcohol, dyes, or sugar added.

VI. Comparative Effectiveness of the Biguanides

Studies specifically for metformin oral solution are available as bioequivalence studies with metformin (Glucophage tablets). Because the oral solution has been shown to be bioequivalent to the oral immediate release tablets, clinical efficacy data available for Riomet is based on study data with metformin tablet formulations. There have been no published efficacy studies specifically for metformin oral solution (Riomet). Table 8 describes efficacy data for metformin.

Table 8. Additional Outcomes Evidence

Study	Sample	Duration	Results
Metformin on cardiac risk factors[37]	n=31	12 weeks	16 patients with type 2 diabetes on diet therapy and 15 on sulfonylurea monotherapy were treated with metformin: • Fasting plasma glucose concentrations decreased to a similar degree after treatment with metformin in both the metformin monotherapy group (12.45 +/- 0.48 vs. 9.46 +/- 0.47mmol/L, P=<0.001) and the combined sulfonylurea plus metformin group (14.09 +/- 0.51 vs. 10.57 +/- 0.85mmol/L, P=0.001). • Fasting plasma lipid concentrations and LDL particle size did not significantly change in either treatment group, whereas fasting remnant lipoprotein cholesterol (RLP-C) concentrations were significantly lower in the metformin monotherapy group (0.43 +/- 0.09 vs. 0.34 +/- 0.07mmol/L, P=0.02). • Concentrations of plasma glucose, free fatty acid, triglyceride, and RLP-C concentrations were lower to a similar degree in both treatment group, whereas daylong plasma insulin concentrations were unchanged. • Fasting plasma soluble molecule-1 (sVCAM-1) levels were significantly lower in both groups, however, fasting plasma soluble intercellular adhesion molecule-1 (sICAM-1) and sE-selectin levels were essentially unchanged.
Pioglitazone compared with metformin[38]	n=205 type 2 diabetics	32 weeks	In a head-to-head study of pioglitazone 30mg (titrated to 45mg as needed) and metformin 850mg (titrated to 2550mg as needed) looking at glycemic control and insulin sensitivity: • Pioglitazone was comparable to metformin in improving glycemic control as measured by HbA1c and fasting plasma glucose. • However, pioglitazone was significantly more effective than metformin in improving indicators of insulin sensitivity, as determined by reduction of fasting serum insulin (P=0.003) and by analysis of homeostasis model assessment for insulin sensitivity (P=0.002). • Both pioglitazone and metformin were well tolerated. • The more pronounced improvement in indicators of insulin sensitivity with pioglitazone, compared with metformin, may be of interest for further clinical evaluation.
Metformin in pediatric patients[39]	n=82 type 2 diabetics age 10-16 years	16 week placebo-controlled trial	In this randomized double blind placebo-controlled trial of metformin at doses up to 1,000 twice daily, the safety and efficacy of metformin was: • The adjusted mean change from baseline in fasting plasma glucose for metformin was –2.4mmol/l compared with +1.2mmol/l for placebo (P<0.001). • Mean HbA1c levels, adjusted for baseline levels, were also significantly lower for metformin compared with placebo (7.5 vs. 8.6%, respectively; P<0.001). • Metformin did not have a negative impact on body weight or lipid profile. • Adverse events were similar to those reported in adults treated with metformin.

Efficacy of metformin-The Multicenter Metformin Study Group[40]	Protocol 1 n = 289 Protocol 2 n = 632	29 weeks	Protocol 1: After 8 weeks of diet therapy, patients were randomized to receive metformin or placebo. Results: As compared to placebo, the metformin group had lower mean fasting plasma glucose concentrations of (189 ± 5 vs. 244 ± 6mg/dl; P<0.001). HbA1c levels were also lower in the metformin group (7.1 ± 0.1% vs. 8.6 ± 0.2%; P<0.001). Protocol 2: Patients were assigned to 1 of 3 treatments-metformin, glyburide, or both metformin plus glyburide. Results: Patients in the metformin plus glyburide combination group, compared to the glyburide alone group, had lower mean fasting plasma glucose concentrations (187 ± 4 vs. 261 ± 4mg/dl; P<0.001, and HbA1c values of 7.1 ± 0.1% vs. 8.7 ± 0.1%; P<0.001). Other endpoints included: • The effect of metformin alone was similar to that of glyburide alone. • 18% of the patients given metformin plus glyburide had symptoms compatible with hypoglycemia, as compared to 3% in the glyburide group and 2% in the metformin group. • In both protocols, in patients given metformin, there was a statistically significant decrease in plasma total and low density lipoprotein cholesterol and triglyceride concentrations, whereas the values in the respective control groups did not change.
Switching from immediate-release metformin to the once daily formulation[35, 41]	n=217 patients already on metformin 500mg BID for at least 8 weeks	24 week randomized, parallel study with a single blind lead in period	In a study designed to evaluate the effect on glycemic control when switching from immediate release metformin to the extended-release product, patients were randomized to 1 of 3 groups: 1) continue on immediate release metformin at the same dose (500mg BID), 2) extended-release metformin 1000mg QD, 3) extended-release metformin 1500mg QD): • At week 12, the mean change from baseline in HbA1c was 0.15% for immediate release metformin, 0.23% for extended-release 1000mg, and 0.04 for the extended-release 1500mg group. The 0.23% in the Glucophage XR 1000mg group was statistically significant. • The corresponding changes at week 24 were 0.06, 0.25, and 0.14.
Triple therapy with metformin, insulin aspart and rosiglitazone[42]	n=16 obese type 2 diabetics	6 months	The effect of triple therapy on patients previously taking human NPH insulin or NPH Mix was studied and showed: • In patients treated with triple therapy versus those continuing on their normal NPH insulin regimens (the control group), HbA1c declined from 8.8% to 6.8% (P<0.01) without inducing severe hypoglycemic events. • In the control group, the insulin dose was increased by 50% with no subsequent change in HbA1c or 24-hour blood glucose profiles. • Insulin sensitivity improved in both skeletal muscle and the lover in the triple therapy group, whereas no change was observed in the control group.
Metformin in type 1 diabetes[43]	n=26 type 1 diabetics, poorly controlled	3 months	In a study looking at whether the addition of metformin improves metabolic control and insulin sensitivity: • HbA1c decreased significantly in the group treated with metformin, versus insulin alone (9.6 to 8.7%; P<0.05). • Peripheral glucose uptake divided by mean plasma insulin concentration was increased in the metformin group (P<0.05) but not in the placebo group. • Initial insulin sensitivity was inversely correlated to changes in HbA1c (P<0.05) and positively correlated to changes in insulin sensitivity (P<0.01).
GI tolerability of XR metformin vs. immediate-release metformin[44]	n=471 (310 metformin XR and 158 metformin immediate-release)	Retrospective chart review	Patients started on extended-release metformin or switched from immediate-release metformin were assessed for GI tolerability in the XR cohort, along with patients started on immediate-release metformin within the previous 2 years. Results showed: • Mean daily doses were 1,258mg for metformin XR and 1,282mg for immediate-release metformin. • 25% of the metformin XR cohort was switched from immediate-release metformin due to GI adverse events. • Despite this, the frequency of any GI adverse event was similar between metformin XR and immediate-release metformin (11.94 % vs. 11.39%, p=0.86).

			• The incidence of individual GI adverse events also did not differ significantly between cohorts. • In one cohort of 205 patients started on immediate-release metformin and switched to metformin-XR, the frequency of any GI adverse event was 26.34% (while taking immediate-release metformin; n=205) vs. 11.71% (after switching to metformin XR; n=205) (p=0.0006). • The frequency of diarrhea in the one cohort mentioned above was 18.05% (while taking immediate-release metformin) vs. 8.29% (after switching to metformin XR) (p=0.0084).

Additional Evidence

Dose Simplification: In a 24 week double-blind, randomized study of metformin XR once daily (1000mg and 1500mg QD), and metformin immediate-release given twice daily (500mg BID), patients were evaluated after 8 weeks of pre-study treatment with metformin 500mg BID for 8 weeks.[35] Table 9 displays the results. At 12 weeks, there was an **increase in HbA1c** in all groups, with the metformin XR 1000mg group having a statistically significant increase of 0.23%.

Table 9. Metformin Immediate-Release vs. Metformin XR[35]

	Metformin 500mg BID	Metformin XR 1000mg QD	Metformin XR 1500mg QD
HgA1C	n=67	n=72	n=66
Baseline	7.06	6.99	7.02
Change at 12 weeks	0.14	**0.23**	0.04
(95% CI)	(-0.03, 0.31)	(0.10, 0.36)	(-0.08, 0.15)
Change at final visit	0.14[a]	0.27	0.13
(95% CI)	(-0.04, 0.31)	(0.11, 0.43)	(-0.02, 0.28)
FPG (mg/dl)	n=69	n=72	n=70
Baseline	210.3	202.8	192.7
Change at 12 weeks	0.4	0.9	0.7
(95% CI)	(-0.4, 1.5)	(0.0, 2.0)	(-0.4, 1.8)
Change at final visit	0.9	**1.1**	0.9
(95% CI)	(-0.4, 2.2)	(-0.2, 2.4)	(-0.4, 2.0)

[a]n=68

Another study looking at adherence indices for metformin and sulfonylureas in 2,920 patients showed that adequate adherence (≥90%) was found in 31% of the prescribed sulfonylureas alone and in 34% of those prescribed metformin alone.[45] There were significant trends of poorer adherence with each increase in the daily number of tablets taken (p=0.001) and increase in co-medication (p=0.0001) for sulfonylureas alone after adjustment for other factors. This study did not look at the long-term impact of adherence issues in this diabetic population.

Yet another study has evaluated adherence to oral antidiabetic agents.[46] This study evaluated medication adherence among patients receiving monotherapy with metformin or glyburide, combination therapy with metformin and glyburide, and fixed-dose combination therapy (glyburide/metformin). There were no significant differences in adherence rates among 6,502 newly treated patients receiving monotherapy, combination therapy, or fixed-dose combination therapy. Among 1,815 patients previously treated with glyburide or metformin monotherapy who required addition of another agent, resulting in combination therapy, adherence rates were significantly lower (54%) than in the 105 patients receiving monotherapy who were switched to fixed-dose combination therapy (77%). Similar results were observed in patients receiving combination therapy who were switched to fixed-dose combination therapy (71% vs. 87%; p<0.001).

Stable Therapy: When transferring from sulfonylurea agents to metformin, a transition period generally is not required, and the sulfonylurea agents may be abruptly discontinued.[24] Close monitoring is necessary during this transition period.
In a randomized trial, patients currently treated with metformin immediate-release were switched to metformin XR.[35] Results of the study showed patients receiving metformin treatment may safely be switched to metformin XR once daily at the same total daily dose, up to 2000mg given once daily.

Impact on Physician Visits: Bristol-Myers Squibb reports no data from studies relating to physician visits or use of medical services with metformin (metformin and metformin XR). A literature search using Medline/Pubmed and Ovid produced limited peer-reviewed data relating to utilization of medical resources with metformin. The data that was pulled was from pharmacoeconomic studies, and evaluated overall costs of treatment for the first-line treatments in diabetes. Because cost information is not a consideration in reviews for the PDL, this data has not been included.

VII. Conclusions

The biguanide medications play an important role in the treatment of diabetes and prevention of diabetes-related complications. There is a wealth of clinical data to support the use of metformin in type 2 diabetes; some data is available for its use in type 1 diabetes. The biguanides offer benefits on glycemic control, have favorable cholesterol profiles, and have been studied in combination with multiple other antidiabetic agents, including insulin. Although metformin extended-release (Glucophage XR) is more conveniently dosed (once-daily) and appears to have a slightly better gastrointestinal adverse effect profile than Glucophage (metformin), clinical efficacy data suggests the products in this class are similar. With the introduction of a generic extended-release metformin 500mg tablet, this formulation is more readily available.

Metformin oral solution (Riomet) offers a new treatment formulation for the biguanide class. There are no clinical advantages of the oral solution other than administration to patients who cannot swallow tablets or are not willing to swallow tablets. These patients are considered a niche population for which authorization of a special dosage form may be granted through the prior authorization program.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics in this class and offer no significant clinical advantage over other alternatives in general use.

VIII. Recommendations

No brand biguanide is recommended for preferred status.

Insulins (AHFS 682008)

I. Comparative Indications of the Insulin Products

Insulin is used as replacement therapy in patients with diabetes, replacing deficient endogenous insulin and temporarily restoring the ability of the body to properly utilize carbohydrates, fats, and proteins. For insulin therapy to be successful, patients must be instructed on the nature of their disease and how to detect complications. Regulation of diet, exercise and body weight should not be disregarded. Although largely used for type 1, insulin dependent diabetes, insulin may be used in type 2 diabetes; in either type, insulin can be administered as either conventional (1-2 injections per day) or intensive (3 or more injections per day) treatment. Table 1 lists the insulin products available for the treatment of diabetes. This review encompasses all dosage forms and strengths.

Clarification: All insulin products have been included in this review for clinical comparison purposes; however, any insulin product that is an OTC is considered a preferred product on the PDL. Therefore, the recommendation made for insulin products in this review pertains only to the prescription insulin products. Table 2 defines the OTC and prescription insulin products.

Table 1. Insulin Products in this Review

Generic Name**	Formulation	Example Brand Names (s)
Insulin aspart	Rapid-acting	Novolog vial and Penfill, Novolog Prefilled Flexpen , Novolog Mix 70/30 vial and Penfill, Novolog Mix 70/30 Prefilled Flexpen
Insulin lispro		Humalog, Humalog Mix 75/25
Insulin (Purified)		Iletin II Regular Purified Pork
Insulin human (Regular)		Humulin R, Humulin R (U-500), Novolin R, Novolin R Penfill, ReliOn R, Novolin InnoLet
Insulin human (Regular) semisynthetic		Velosulin BR Human
Insulin (regular)	Short-acting	-
Insulin human zinc (Lente), recombinant DNA origin	Intermediate-acting	Humulin L, Novolin L*
Isophane insulin human (NPH), recombinant DNA origin		Humulin N, Humulin N Pen, Novolin N, Novolin N Penfill, Novolin InnoLet, ReliOn N, ReliOn N Novolin InnoLet
Insulin human combinations, recombinant DNA origin		Humulin 70/30, Humulin 70/30 Pen, Novolin 70/30, Humulin 50/50, Novolin 70/30 Penfill, Novolin InnoLet, ReliOn 70/30, ReliOn 70/30 Novolin InnoLet
Insulin, isophane		Iletin II NPH Purified Pork
Insulin Zinc (purified)		Iletin II Lente Purified Pork
Insulin glargine	Long-acting	Lantus
Extended insulin human, zinc (recombinant DNA origin)		Humulin U Ultralente

*Novolin L was discontinued 10-2003. **No generic insulins are available.

There are two main pharmaceutical companies producing insulin products: the Humulin line of products is from Eli Lilly and the Novolin products are from Novo Nordisk. The ReliOn / Novolin products are manufactured for Wal-Mart by Novo Nordisk. Lantus, from Aventis, is the newest product in the class. The Novo Penfill products are for use with the NovoPen 3, NovoPen Junior, InDuo, and Innovo insulin delivery devices. The Penfill products are only available as 3ml cartridges; the 1.5ml are no longer available. Novolin InnoLet is available in regular, NPH and 70/30 insulin, while the ReliOn InnoLet is only available in NPH and 70/30 insulin. Although the product lines are similar, there are a few distinctions:

- Novolin insulins are produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae* (bakers yeast). In comparison, Humulin insulins are produced from a non-pathogenic strain of *Escherichia* coli, that has been genetically altered by the addition of the gene for insulin lispro.
- Eli Lilly has the Humulin Ultralente product. There is not a comparable Novo Nordisk product. However, use of Lantus and twice daily NPH regimens is more common.

- The ultra-short acting products (Novolog and Humalog) are clinically similar, despite some pharmacokinetic differences.
- While the Novo Nordisk product line does not have a product similar to Lilly's Humulin 50/50, this mixture could be obtained using combined doses of Novolin R and Novolin N.
- Eli Lilly's product line lacks a comparable product to Novo's Velosulin BR Human, which has limited use by diabetic patients using insulin pumps. However, Novolog is FDA approved for use in external insulin pumps. In comparison, Humalog is not approved for use in insulin pumps, but has been extensively used and studied for this purpose.
- Humulin L stands alone as the single insulin human zinc product; Novo Nordisk has discontinued their Novolin L product as of October 2003.
- The ReliOn product line, from Wal-Mart, mirrors the products from Novo Nordisk (with the exception of InnoLet). ReliOn products are considered multi-source brands.

Most available insulin products are indicated for general use in diabetes mellitus. A few have specific indications based on their pharmacokinetic actions or use in insulin pumps.

Table 2. FDA-Approved Indications for the Insulin Products; Ranked Rapid-Acting to Long-Acting[3,24, 47]

Product	Adults with Diabetes, for the Control of Hyperglycemia	Insulin Pump Use	Non-Specific Treatment of Diabetes	Other Indication/s	OTC vs. Rx
Novolog	✓	✓			Rx
Novolog Mix 70/30			✓		Rx
Novolog Penfill	✓				Rx
Humalog	✓			Type 2:use with oral agents;Type 1 in combo with a longer acting insulin	Rx
Novolog / Novolog Mix Flexpen			✓		Rx
Humalog Mix 75/25	✓				Rx
Iletin II Regular pork			✓		OTC
Humulin R			✓		OTC
Humulin R (U-500)				Insulin resistance with daily need > 200 units	Rx
Novolin R			✓		OTC
Novolin R Penfill			✓		OTC
ReliOn R			✓		OTC
Velosulin BR Human		✓		With U-100 insulin syringes	OTC
Humulin L			✓		OTC
Novolin L			✓		OTC
Humulin N			✓		OTC
Novolin N			✓		OTC
Humulin N Pen			✓		OTC
Novolin N Penfill			✓		OTC
ReliOn N			✓		OTC
Humulin 70/30			✓		OTC
Humulin 70/30 Pen			✓		Rx
Novolin 70/30			✓		OTC
Humulin 50/50			✓		OTC
Novolin 70/30 Penfill			✓		OTC
ReliOn 70/30			✓		OTC
Iletin II NPH			✓		OTC
Insulin NPH			✓		OTC

Iletin II Lente			✓		OTC
Insulin Lente			✓		OTC
Lantus				QD SQ use in adults and children with Type 1 & type 2 diabetes	Rx
Humulin U Ultralente			✓		OTC

II. Pharmacokinetic Parameters

The main differences among the available insulin products occur in the onset and duration of action. Some insulins can be mixed for better control of glucose levels, and insulin can be beneficial in type 2 diabetes when used with oral antidiabetic agents.

Absorption

Following administration of insulin, the injection is absorbed directly into the blood. Experimentation of other routes of administration such as intranasal, transdermal, and oral inhalation have been studied in a limited number of patients. Exubera, an inhaled insulin, is being co-developed by Aventis and Pfizer, and Novo Nordisk is developing a product of their own. These products are not currently available and will be reviewed when they become eligible. The rate of absorption depends on many factors including: route of administration, site of injection, volume and concentration of the injection, and insulin type. One study showed that insulin administered intramuscular (IM) resulted in more rapid absorption.[3] Presence of insulin-binding antibodies may be another contributor to delay or reduction in absorption. Human insulins may have a more rapid onset and shorter duration of action than porcine insulins. Table 3 compares the various types of insulin preparations, by half-life, onset, peak, duration and compatibility. The pharmacokinetics of Lantus (insulin glargine) allows for once daily administration.

Table 3. Pharmacokinetic Parameters and Compatibility of Various Insulins[24]

Insulin Preparations		Half-Life	Onset (hrs)	Peak (hrs)	Duration (hrs)	Compatible mixed with
Rapid-Acting	Insulin (regular)	-	0.5-1	-	8-12	All
	Prompt insulin zinc susp.	-	1-1.5	5-10	12-16	Lente
	Insulin Lispro	1	0.25	0.5-1.5	2-5	Ultralente, NPH
	Insulin Aspart	1.5	0.25	1-3	3-5	[1]
Intermediate-Acting	Isophane, insulin (NPH)	-	1-1.5	4-12	24	Regular
	Zinc, insulin Susp. (Lente)	-	1-2.5	7-15	24	Regular, Semilente
Long-Acting	Insulin glargine	-	1.1	5[2]	24[3]	None
	Protamine insulin zinc susp.	-	4-8	14-24	36	Regular
	Extended insulin zinc susp.	-	4-8	10-30	20-36	Regular, Semilente

[1] See detailed Administration and dosage in insulin aspart monograph.

[2] No pronounced peak; small amounts of insulin glargine are slowly released resulting in a relatively constant concentration/time profile over 24 hours.

[3] Studies only conducted up to 24 hours.

Distribution, Metabolism and Elimination

Insulin is rapidly distributed throughout extracellular fluids and has a plasma half-life of a few minutes in healthy individuals. Elimination may be prolonged in diabetic patients, as a result of binding of the hormone to antibodies, and in patients with renal impairment. Insulin is rapidly metabolized mainly in the liver by glutathione insulin transhydrogenase. Once in the kidneys, insulin is 98% reabsorbed in the proximal tubule, with 40% of this reabsorbed insulin being returned to venous blood.

After subcutaneous injection of insulin glargine (Lantus), serum concentrations indicate a slower, more prolonged absorption and relatively constant concentration/time profile over 24 hours with no pronounced peek in comparison to NPH human insulin. However, the manufacturer states in a study comparing once-daily insulin glargine to once and twice-daily NPH insulin, overall rates of hypoglycemia did not differ between patients with diabetes treated to insulin glargine compared with NPH insulin.[47]

III. Drug Interactions with Insulins

Common:
Anabolic steroids and beta-blocking agents have effects on glucose metabolism. Both may impair glucose tolerance or increase the frequency or severity of hypoglycemia. Beta-blockers may suppress hypoglycemia-induced tachycardia but not hypoglycemic sweating, delay the rate of recovery of blood glucose concentration following drug-induced hypoglycemia, alter the hemodynamic response to hypoglycemia, and possibly impair peripheral circulation. Nonselective beta-blockers (e.g. propranolol, nadolol) are more likely to affect glucose metabolism than more selective agents (e.g. metoprolol, atenolol).

The hypoglycemic activity of insulin may be potentiated by concomitant administration with alcohol, monoamine oxidase inhibitors, guanethidine, oral hypoglycemic agents, salicylates, sulfa antibiotics, certain ACE-inhibitors, and inhibitors of pancreatic function (e.g. octreotide).[3]

Drugs with a tendency to produce hyperglycemic activity that can antagonize the activity of insulin and exacerbate glycemic control include calcium-channel blocking agents, niacin, corticosteroids, estrogens, oral contraceptives, isoniazid, phenothiazines, sympathomimetics, thiazide diuretics, furosemide, ethacrynic acid, and thyroid hormones.

Drug interactions are consistent for the insulins as a class. There are not advantages of certain insulin products over others with regards to drug interactions. Table 4 further describes the most clinically severe, level 1 (rapid onset, major severity) drug interactions for the insulins. Previous mentioned drug interactions, although less severe, should be monitored and dosage adjustments may be necessary for insulin or for the precipitating drug.

Table 4. Clinically Significant Drug Interactions [23]

Significance	Interaction	Mechanism
1	Insulin and Ethanol	Enhanced release of insulin following a glucose load and inhibition of gluconeogenesis potentiates the glucose-lowering action of insulin. Moderation of ethanol intake, taken with a meal, is important in preventing this interaction.

IV. Adverse Drug Events of the Insulin Products

Adverse events with the insulin products are rare and occur similarly as a class. Most adverse reactions that do occur are related to the injection site. Few people with diabetes develop red, swollen and itchy skin where insulin has been injected, often a sign of improper injection.[3] Patients with uncontrolled blood glucose concentrations for extended periods of time, or in patients in whom rapid glycemic control has been achieved, may develop transient blurred vision when given insulin. The blurred vision is a result of the osmotic equilibrium between the lens and ocular fluids; visual acuity stabilizes with time.

Generalized insulin allergy occurs rarely, but when it does it may cause a serious reaction, including a skin rash over the body, shortness of breath, fast pulse, sweating, and a drop in blood pressure.[47] When insulin allergies have occurred, patients would be skin-tested with each new insulin preparation before it is used.

The literature contains multiple studies and articles comparing the incidence of hypoglycemia with NPH insulin and insulin glargine (Lantus). With NPH insulin, peak insulin activity occurs 4-6 hours following administration; therefore, nocturnal hypoglycemia commonly takes place after bedtime administration.[48] The manufacturer of insulin glargine (Lantus) reports in the product information at least 4 studies in type 1 and type 2 diabetic patients that have indicated the overall rates of hypoglycemia between insulin glargine (Lantus), and NPH and regular insulin is similar.[47]

V. Dosing and Administration for Insulin Therapy

Insulin is usually administered by subcutaneous injection in the thighs, upper arm, buttocks, or abdomen. However, regular insulin can be administered IV or IM in the treatment of diabetic ketoacidosis.[3] Injections should be made using only syringes calibrated for the correct insulin concentration.

Dosage of insulin is expressed in USP units. The number of units in a given volume varies with the strength of the preparation, with commercially available products with 100 (U-100) or 500 (U-500) units per ml. Conventional insulin therapy usually consists of a mixture of intermediate-acting and rapid-or short-acting insulin, given in 1-2 injections per day. Intensive insulin therapy consists of 3 or more doses of insulin per day or continuous insulin via an insulin pump. For the most part, insulin pumps are reserved for patients with diabetes who are not well controlled with 3-4 daily insulin injections.

Other insulin delivery devices have been developed and are available to help patients administer insulin. Prefilled pens offer simplicity, with minimal training and attention required, and no installation of new cartridges. One study of 121 patients age 28-81, comparing use of a normal insulin vial and syringe versus use with a prefilled, disposable pen (Flexpen), assessed patient preferences between the two methods of insulin administration.[49] Seventy-four percent of patients indicated a preference for the pen over the vial/syringe method. Eighty-Five percent considered the pen more discreet for use in public, 74% considered it easier to use overall, and 85% found the insulin dose scale on the pen easier to read. During the study, patients had significant improvement in HbA1c values ($P<0.05$). However, no significant differences in fasting plasma glucose, mean 4-point blood glucose profiles, or serum fructosamine values were found between groups.

Initial total daily insulin doses in adults and children with type 1 diabetes range from 0.2-1 units/kg (generally 0.5-0.8 units/kg daily). Basal insulin requirements with an intermediate-acting or long-acting insulin usually comprise 40-60% of the total daily insulin dosage, with the remainder given as rapid or short-acting insulin. A typical insulin regimen might consist of 1-2 injections of intermediate-acting insulin before breakfast and/or before dinner in conjunction with doses of a rapid or short-acting insulin before each meal. Specifically, Lantus (insulin glargine) is given as a once daily subcutaneous injection once daily at bedtime, making administration with Lantus advantageous over other insulins. Sometimes, in patients with severe metabolic dysfunction, hospitalization and the use of regular insulin is necessary. Patients with ketosis, illness, or children in a growth phase may require an initial insulin dosage of 1-1.5 units/kg daily. Obese individuals and those with insulin resistance can require up to 0.7-2.5 units/kg daily. Insulin doses should be increased by 10-20% of the previous dose every several days to once a week, based on each individual patient's requirements and response.

Special Dosing Considerations

- When a brand of insulin becomes unavailable, the same insulin formulation from another manufacturer may be substituted.
- When therapy with a different insulin is started (different strength, brand, type, or species), it is known that a limited number of patients will require a change in insulin dosage (although it is not possible to clearly identify which patients require a change).
- Insulin glargine must not be mixed with other medicinal product or residue.

- The safety and effectiveness of insulin glargine has been established in the age group 6-15 years with type 1 diabetes. The drug is only indicated for use in adult patients with type 2 diabetes who require basal insulin for control of hyperglycemia.

VI. Comparative Effectiveness of the Insulin Products

The DCCT trial, which demonstrated the benefits of intensive insulin treatment in type 1 diabetics, has been one of the most influential and important trials in type 1 diabetes.[13] When intensive treatment is started early, the rate of progression of complications is less compared to that among the conventional treatment group. Intensive therapy methods were defined as 3 or more daily injections or use of an insulin pump, 4 or more blood glucose tests daily, dietary instruction to help achieve goals, monthly clinic visits, and integrated team care. Insulin types used were not specified. There is no question that insulin therapy is important to the treatment of diabetes. Studies have been presented in each section of this monograph supporting use of insulin with oral antidiabetic agents. Recently published studies have looked at the impact of treatment with insulins.

Table 5. Additional Outcomes Evidence for Insulins

Study	Sample	Duration	Results
18 years of fair glycemic control preserves autonomic function in type 1 diabetes[50]	n=39	18 years	In looking at the association between HbA1c and cardiac autonomic function with intensive insulin therapy, in patients with a HbA1c <8.4% (low) and in those with a HbA1c >8.4% (high): • All cardiac autonomic tests were significantly different in the high and low HbA1c groups, with the most favorable scores seen in the low HbA1c group. • Minimal heart rate at night was significantly lower in the low HbA1c group compared to the high group (P=0.039). • With maximal exercise, the increase in heart rate was significantly higher in the low HbA1c group vs. the high group (P=0.001).
Early glycemic control, age at onset, and dev. of microvascular complications in children with type 1 diabetes[51]	n=94	12 years	Studying the impact of glycemic control (HbA1c), with intensive insulin therapy, early in disease and age at onset on the occurrence of incipient diabetic nephropathy and retinopathy resulted in: • Glycemic control was significantly associated with both diabetic nephropathy and retinopathy when adjusted for sex, birth weight, age at onset, and tobacco use confounders. • Mean HbA1c during the first 5 years of diabetes was a near-significant determinant for the development of diabetic nephropathy (P=0.083) and a significant determinant of retinopathy (P=0.036). • The age of onset of diabetes significantly influences the risk of developing retinopathy (P=0.015), but there was no clear tendency for diabetic nephropathy.
Insulin analogues versus NPH and regular human insulin in basal-bolus therapy in type 1 diabetes[52] *This study was performed in Australia. Insulin detemir is a long-acting insulin analog,	n=595 Note: Insulin	18 weeks	When patients were randomized to either insulin detemir (a long-acting insulin analog*) or NPH insulin in the morning and at bedtime in combination with mealtime insulin aspart of regular insulin: • Glycemic control with detemir/insulin aspart was improved in comparison with NPH/regular human insulin (HbA1c 7.88% vs. 8.11%, P<0.001). • Self-measured 8-point plasma glucose profiles differed between the groups (P<0.001), with lower postprandial plasma glucose levels in the detemir/insulin aspart group. • Day-to-day variation in plasma glucose was lower with the detemir/insulin aspart group as compared to the other group (P<0.001). • Overall risk (P=0.036) and nocturnal hypoglycemia (P<0.001) was 21% and 55% lower in the insulin detemir/insulin aspart group than in

similar to insulin glargine. It is not FDA approved in the U.S., but has received an Approvable Letter from the FDA.	detemir has not been approved and will be reviewed when eligible.		the NPH/ regular insulin group. • Body weight was 1kg lower with insulin detemir/insulin aspart than with NPH insulin/regular insulin group (P<0.001).
Insulin lispro vs. regular insulin in children[53]	n=35	3 month crossover study	In a cross over study of 35 children age 5-10 years, participants were given insulin lispro for 3 months and regular insulin for 3 months in addition to their intermediate-acting insulin: • HbA1c after 3 months on insulin lispro (8.33%) was not significantly different to that on regular insulin (8.14%). • No significant differences were found in blood glucose levels before or after meals, 2-hour postprandial glucose excursions or in blood glucose levels before bed, between the treatments. • Blood glucose levels at 3am were significantly lower on regular insulin than on insulin lispro (P=0.01).
Insulin pump in pediatrics[54]	n=161	3 years	In examining the efficacy and safety of using continuous subcutaneous insulin infusion (CSII) in children aged 18 months to 18 years: • There was a significant and consistent reduction in mean HbA1c levels after 12 months of CSII (P<0.02). • Improved diabetes control was achieved with CSII without increasing daily insulin doses and in association with a decrease in the frequency of severe hypoglycemic events (P<0.05) vs. prepump.
NPH insulin QID vs. insulin glargine QD[55]	n=51	3 months	Patients on NPH intensive therapy (injections QID) plus lispro insulin at each meal, were randomized to 3 different regimens of basal insulin substitution while continuing lispro insulin at meals: 1) continuation of NPH QID 2) QD insulin glargine at dinnertime or 3) QD insulin glargine at bedtime. Results showed: • Mean daily blood glucose was lower with dinnertime insulin glargine or bedtime insulin glargine versus NPH (P<0.05). • A greater percentage of blood glucose values were at target value with insulin glargine at dinner and bedtime versus those with NPH (P<0.05). • HbA1c at 3 months did not change with NPH but decreased with insulin glargine at both dinnertime and at bedtime (P<0.04). • Frequency of mild hypoglycemia was lower with insulin glargine than with NPH (P<0.04). • Outpatient blood glucose data indicated more steady plasma insulin concentrations at night and before meals with insuin glargine versus NPH (P<0.05). • There were no significant differences in insulin glargine given at dinnertime versus at bedtime.
HOE 901, The U.S. insulin glargine type 1 diabetes investigative group[56]	n=256	4 weeks	In evaluating the safety and efficacy of insulin glargine in type 1 diabetes, patients were randomized to receive NPH insulin once daily at bedtime or twice daily (breakfast and bedtime), or insulin glargine QD at bedtime: • The insulin glargine group had significantly lower fasting glucose levels than the NPH group, with adjusted mean fasting plasma glucose levels reduced by 2.2mmol/l (P=0.0001). • Insulin glargine was superior to NPH in reducing fasting plasma glucose levels in patients who had previously received NPH twice daily, but not in patients who had previously received NPH once daily. • Fasting plasma glucose levels were more stable in patients using insulin glargine than in patients using NPH insulin.
Insulin glargine (Lantus) QD at bedtime vs. NPH QD and BID insulin[47]	n=2327 adults & n=349 pediatric patients with type 1 diabetes;	Rando-mized, active-control, parallel study	The safety and effectiveness of insulin glargine and NPH insulin were compared: • Reduction in HbA1c with Lantus was similar to that with NPH human insulin. • Overall rates of hypoglycemia did not differ between patients with diabetes treated with Lantus compared with NPH.

	1563 adults with type 2 diabetes		
Insulin glargine (Lantus) or human NPH insulin added to oral therapy in type 2 diabetes[57]	n=756	24 week multi-center study	When once daily insulin glargine (Lantus) or human NPH insulin was added to oral therapy in type 2 diabetics to achieve goal HbA1c of 7%: • Mean fasting plasma glucose at endpoint was similar with both insulin groups, as was HbA1c. • A majority of patients reached goal HbA1c with each type of insulin. • 25% more patients attained goal HbA1c without documented nocturnal hypoglycemia with insulin glargine (Lantus) compared to NPH insulin ($P<0.05$). • Rates of other categories of symptomatic hypoglycemia were 21-48% lower with insulin glargine (Lantus).
Insulin glargine in children and adolescents with type 1 diabetes[58]	n=71	12 month retrospective analysis	In evaluating the medical records of 71 children with type 1 diabetes who initiated treatment with insulin glargine therapy, data was collected for 6 months before and 6 months after the addition of insulin glargine. Results indicated: • The total daily long-acting insulin dose decreased by about 20% after initiating insulin glargine therapy. • There were no significant differences in HbA1c and blood glucose control prior to and after initiation of insulin glargine therapy (HbA1c at baseline 8.9 +/- 1.6% and HbA1c after 6 months of insulin glargine therapy was 8.9 +/- 1.5%). • Overall, blood glucose concentrations did not differ significantly throughout the study. • However, patients who switched to glargine because of nocturnal hypoglycemia had a 65% decrease in nocturnal blood glucose reading less than 50mg/dL.
Humalog and Humalog mix provide better glycemic control than insulin glargine in type 2 diabetes[59]	n=159	6 month randomized, prospective open label study	In order to analyze the effect of three-times daily Humalog (HL) or Humalog mix 50 (HM) versus once-daily insulin glargine (L) on glycemic control, patients were randomized to one of the three treatment regimens: • After 6 months, the HL and HM groups showed significantly lower blood glucose excursions after breakfast than the L group ($p<0.0001$ vs. HL, $p=0.0006$ vs. HM, respectively). • At 6 months, HbA1c had improved by 1.1% in the HL group, by 1.2% in the HM group, and by 0.3% in the L group ($p\leq0.001$ for HM and HL vs. L). • No relevant treatment differences were observed with respect to the number of hypoglycemic events, although the daily insulin dose at the end of the study was higher in the HL or HM group compared to the L group.

Additional Evidence

Dose Simplification: Although no peer reviewed studies on adherence in diabetic patients specifically looked at treatment with insulins, one retrospective analysis showed that young patients filled prescriptions for one-third of prescribed insulin doses.[60] Adherence to insulin among patients with type 2 diabetes was 62-64%. In another study, researchers found that for each 10% increment in drug adherence, HbA1c decreased by 0.16% ($p<0.0001$).[61] Aventis Pharmaceuticals reports no studies have been done with insulin glargine (Lantus) with regards to better adherence with the drug's once-daily dosing.

Stable Therapy: When changing treatment regimen with an intermediate or long-acting insulin to a regimen with insulin glargine, the amount and timing of short-acting insulin or fast-acting insulin analog or the dose of any oral antidiabetic drug may need to be adjusted. In studies, when patients were transferred from once-daily NPH insulin or ultralente human insulin to once-daily insulin glargine, the initial dose was usually not changed. When patients were transferred from twice-daily NPH insulin to insulin glargine once-daily, to reduce the risk of hypoglycemia, the initial dose was reduced by approximately 20% and adjusted based on patient response.[47]

Impact on Physician Visits: In a literature search in Medline/Pubmed and Ovid, no peer reviewed studies were found that looked specifically at treatment with insulins and the impact on physician resources utilized. Aventis Pharmaceuticals also reports no pharmacoeconomic studies have evaluated the impact of insulin glargine on physician office visits.

VII. Conclusions

The differences among the insulin products revolve around their onset and durations of action. The available insulin delivery devices (Flexpen, InnoLet, Novopen 3, etc) offer convenience in insulin administration. The Novo Nordisk and Eli Lilly products lines offer similar treatment options. Insulin glargine (Lantus) is conveniently dosed once daily and may have a lower incidence of hypoglycemia compared to NPH insulin, however, large studies have not consistently shown a true clinical superiority on glycemic control with insulin glargine (Lantus) compared to NPH insulin. We recognize there are differences in pharmacokinetic parameters and adverse events between some of the insulins. At this time, however, a single insulin product has not been shown to be clinically advantageous (e.g. statistically significant impact on HbA1c) over another product. Additionally, all OTC insulin products are covered independent of the PDL.

Therefore, all brand prescription products within the class are comparable to each other and offer no significant clinical advantage over other alternatives in general use.

VIII. Recommendations

No brand insulin is recommended for preferred status.

Meglitinides (AHFS 682016) Single Entity Agents

I. Comparative Indications of the Meglitinide Agents

The meglitinides are insulinotropic antidiabetic agents. They are structurally unrelated to sulfonylurea antidiabetic agents, although repaglinide produces reductions in fasting plasma glucose and HbA1c values that are similar to those with sulfonylureas.[3] The meglitinides do not have cross-allergenicity with sulfonamide drugs, as the sulfonylureas do. Functioning β-cells are required for meglitinide hypoglycemic activity, as these drugs lower blood glucose concentrations by augmenting endogenous insulin secretion from the pancreas in response to meals.

The exact mechanism of action of the meglitinides has been demonstrated *in vitro* in studies. The meglitinides inhibit ATP-sensitive potassium channels, increasing intracellular concentrations of calcium, and stimulating insulin release.[47] However, they do not stimulate insulin release in the absence of glucose, and insulin release is diminished at low glucose concentrations. As a result, these drugs have little effect on serum insulin concentrations between meals and overnight. In addition, most of the insulinotropic activity of these drugs is exerted at intermediate glucose concentrations (54-180mg/dl), while at high glucose concentrations (>270mg/dl), the meglitinides do not augment insulin release already stimulated by high extracellular glucose concentrations.

There are two agents available in this class. Table 1 lists the brand and generic names of the products. This review encompasses all dosage forms and strengths.

Table 1. Meglitinide Products in this Review

Generic Name*	Formulation	Example Brand Name
Repaglinide	Oral	Prandin
Nateglinide	Oral	Starlix

*There are no generic formulations available for any of the medications in this class.

Patients whose hyperglycemia is not adequately controlled with glyburide or other insulin secretagogues should not be switched to a meglitinide agent, nor should a meglitinide be added to their treatment regimen. The meglitinides should not be used in patients with type 1 diabetes or in those with diabetic ketoacidosis. Indications for repaglinide and nateglinide are further described in Table 2. When combination therapy with the meglitinides and metformin or a thiazolidinedione (only repaglinide is indicated with thiazolidinediones) is ineffective in achieving glucose control, consideration should be given to discontinuation of the oral drugs and using insulin. As with most oral hypoglycemic agents, treatment should be in addition to diet and exercise, not as a substitute.

Table 2. FDA-Approved Indications for the Meglitinides[47]

	Monotherapy in Type 2 diabetes	Combination Therapy with Metformin	Combination Therapy with Metformin or Thiazolidinediones
Repaglinide (Prandin)	✓*	-	✓
Nateglinide (Starlix)	✓*	✓	-

*When hyperglycemia cannot be controlled with diet and exercise and in those not chronically treated with other antidiabetic agents.

II. Pharmacokinetic Parameters

Absorption
Both repaglinide and nateglinide are rapidly and completely absorbed from the GI tract following oral administration. Peak plasma drug concentrations are seen with repaglinide and nateglinide within 1 hour.[3] When given after meals, nateglinide absorption is delayed in time to peak plasma concentration (T_{max}). Repaglinide pharmacokinetics are also affected by gender, administration with food, and hepatic or renal impairment, but do not appear to be influenced by age. When given with food, repaglinide administration resulted in reduced GI absorption by up to 12.4%; time to peak plasma concentration and mean peak plasma concentration were reduced by up to 30 and up to 20%, respectively.

Distribution, Metabolism and Elimination
Nateglinide is extensively bound to serum proteins (98%) and is extensively metabolized by cytochrome P-450 (CYP) 2C9 (70%) and to a lesser extent CYP3A4 (30%). As with nateglinide, protein binding with repaglinide exceeds 98%. Metabolism of repaglinide occurs by the cytochrome P-450 (CYP) microsomal isoenzyme 3A4. The primary route of elimination for nateglinide is renal, whereas repaglinide is primarily eliminated through bile and excreted via feces. No dosage adjustments are necessary for mild renal or hepatic insufficiency with either drug, however, since these drugs are metabolized in the liver, extreme caution should be used in patients with moderate-to-severe hepatic insufficiency.

Table 3. Pharmacokinetic Parameters of the Meglitinides[3, 47]

	Time to Stimulate insulin	Peak insulin levels	T_{max}	Absolute Bioavailability	Metabolism	Elimination
Repaglinide	30 minutes	1.5 hours, with plasma insulin levels remaining elevated for approx. 4 hours	1 hour	56%	Liver	Mainly through bile: within 96 hours of dose, 90% of dose is excreted in feces
Nateglinide	20 minutes	1 hour, with a fall to baseline by 4 hours after dose	1 hour	73%	Liver	Mainly kidneys: within 6 hours of dose, 83% of dose is recovered in urine

III. Drug Interactions with the Meglitinides

Both meglitinide drugs are metabolized by cytochrome P-450 pathway, although their primary metabolizing enzymes are different. Interactions with nateglinide appear to be less documented in the literature, than those reported with repaglinide.

Nateglinide (Starlix)
Nateglinide has been studied concomitantly with the following drugs and no clinically relevant alterations were discovered: glyburide, metformin, digoxin, warfarin, and diclofenac. Because nateglinide is highly bound, *in vitro* studies have looked at the affect of concomitant use with other drugs that are highly protein bound.[47] The following drugs were evaluated in displacement studies with nateglinide and no influence was found on either nateglinide or the precipitating drugs: furosemide, propranolol, captopril, nicardipine, pravastatin, glyburide, warfarin, phenytoin, acetylsalicylic acid, tolbutamide, and metformin.

However, caution should be used with nateglinide and drugs that may potentiate the hypoglycemic action of nateglinide: NSAIDs, salicylates, MAOI drugs, and nonselective beta-blockers.[23]

Certain drugs may reduce the hypoglycemic action of nateglinide and include: thiazide diuretics, corticosteroids, thyroid products, and sympathomimetics.[23]

Repaglinide (Prandin)
Repaglinide has the potential for interaction with inducers and inhibitors of the cytochrome P450 3A4 isoenzyme. These interactions are well documented in the literature and are further described in Table 4.[3, 23, 47] Repaglinide has similar cautions as with nateglinide when used concomitantly with drugs that are highly protein bound. Patients on highly protein bound drugs should be monitored closely.

3A4 Inhibitors	3A4 Inducers
Azole antifungals (Nizoral, Sporanox)	Rifampin (Mycobutin, Rifadin)
Macrolide antibiotics (Biaxin, erythromycin)	Barbiturates
	Carbamazepine

Table 4. Well Documented Drug Interactions with Repaglinide[23]

Significance	Interaction	Mechanism
2 Delayed, Moderate, Suspected	Repaglinide and Rifamycins	Rifamycins may increase metabolism (CYP3A4) of repaglinide during the first-pass and elimination phases, causing plasma concentrations of repaglinide to be decreased. The dose of repaglinide may need to be adjusted.
2 Delayed, Moderate, Suspected	Repaglinide and Macrolide Antibiotics	Certain macrolide antibiotics may inhibit the first-pass metabolism of repaglinide, causing elevated plasma levels of repaglinide, increased pharmacologic and adverse effects.
4 Delayed, Moderate, Possible	Repaglinide and Azole Antifungals	Certain azole antifungals may inhibit metabolism of repaglinide, causing elevated plasma levels of repaglinide, increasing the pharmacologic effects.
4 Delayed, Moderate, Possible	Repaglinide and Tequin	Exact mechanism is unknown. The effect is severe and persistent hypoglycemia. Until further information is available, Tequin (gatifloxacin) in patients taking repaglinide, should be avoided when possible.

IV. Adverse Drug Events

In clinical trials, repaglinide has been administered to 2,931 patients and studied for 3-months to 1 year. In one study of repaglinide versus treatment with a sulfonylurea, 13% of repaglinide patients were discontinued due to adverse events, compared to 14% of patients on sulfonylureas.[47] The most common adverse drug events with repaglinide include hyper and hypoglycemia, and related symptoms. Mild to moderate hypoglycemia occurred in 16% of repaglinide patients, 20% of glyburide patients, and 19% of glipizide patients.

In clinical trials with nateglinide, 2,400 patients with type 2 diabetes were treated for 6 months to 1 year or longer. Hypoglycemia was uncommon in all treatment groups. Only 0.3% nateglinide patients discontinued due to hypoglycemia.[47] Gastrointestinal adverse events were more common in nateglinide plus metformin than in patients taking only metformin alone.

Table 5. Common Adverse Events (%), by System, Reported for the Meglitinides[47]

Adverse Event	Repaglinide n=352	Placebo n=108	Nateglinide n=1,441	Placebo n=485
Metabolic				
Hypoglycemia	31	7	2.4	0.4
Musculoskeletal				
Arthralgia	6	3	3.3	2.2
Back Pain	5	4	4	3.7
Respiratory				
URI	16	8	10.5	8.1
Sinusitis	6	2	N/A	N/A
Rhinitis	3	3	N/A	N/A
Bronchitis	2	1	2.7	2.6
Gastrointestinal				
Nausea	5	5	N/A	N/A
Diarrhea	5	2	3.2	3.1
Constipation	3	2	N/A	N/A
Vomiting	3	3	N/A	N/A
Dyspepsia	2	2	N/A	N/A
Other				
Headache	11	10	N/A	N/A
Paresthesia	3	3	N/A	N/A
Chest Pain	3	1	N/A	N/A
Urinary Tract Infection	2	1	N/A	N/A
Tooth Disorder	2	0	N/A	N/A
Allergy	2	0	N/A	N/A

N/A Incidence not available

V. Dosing and Administration

There is no fixed dosage regimen with repaglinide. It is important that patient's monitor their blood glucose to determine the minimum effective dose, to detect primary failure (inadequate lowering of blood glucose on the maximum recommended dose), and to detect secondary failure (loss of an adequate blood glucose-lowering response after an initial period of effectiveness. Repaglinide is usually taken within 15 minutes of the meal , but may vary from immediately preceding the meal to as long as 30 minutes before the meal. Dosage adjustments should be made at one week intervals. Dosing for combination therapy with metformin or a thiazolidinedione are the same.

Starlix should be taken 1-30 minutes prior to meals.

Table 6. Dosing for the Meglitinides[47]

	Availability	Dose /Frequency/Duration
Repaglinide	0.5mg, 1mg, and 2mg tablets	Starting dose: 0.5mg with each meal (if HbA1c<8% and no previous treatment) 1-2mg with each meal (if HbA1c≥8% and previously treated with blood glucose-lowering agents) Maximum dose: 4mg with meals, not to exceed 16mg daily)
Nateglinide	60mg and 120mg tablets	Starting and maintenance dose as monotherapy or in combination with metformin: 120mg TID before meals Note: The 60mg dose should be reserved for patients who are near goal HbA1c when treatment is initiated.

Special Dosing Considerations

Renal Impairment:

- For repaglinide, dosing adjustment does not appear to be necessary for patients with mild-moderate renal dysfunction. Patients with severe renal impairment should start therapy with the 0.5mg dose.
- No dosage adjustments are necessary with nateglinide in patients with mild to severe renal insufficiency.

Hepatic Impairment:

- Repaglinide should be used with caution in patients with impaired liver function and longer intervals between dose adjustments should be utilized.
- No dosage adjustments are necessary with nateglinide in patients with mild hepatic insufficiency. However dosing in moderate to severe hepatic disease has not been evaluated.

Other:

- No studies have been performed with repaglinide or nateglinide in pediatric patients.
- Repaglinide and nateglinide are both pregnancy category C drugs.
- Per Novo Nordisk, repaglinide efficacy and bioequivalence has not been studied when crushed or broken. Additionally, repaglinide is not recommended to be given per tube because the drug's mechanism of action relies on a fully functional gastrointestinal tract.
- Per Novartis, nateglinide tablets have not been studied in a crushed form and as a result, it is recommended nateglinide tablets be used in their whole intact form.

VI. Comparative Effectiveness of the Meglitinides

No head-to-head studies have compared repaglinide and nateglinide, although a combination trial with metformin compared their efficacy. Recent and important clinical efficacy data is described for the meglitinides below.

Table 7. Additional Outcomes Evidence for the Meglitinides

Study	Sample	Duration	Results
Nateglinide 60 or 120mg TID vs. glyburide 10mg QD[47]	-	24 week, double-blind, active control trial	Patients previously treated with a sulfonylurea and with a HbA1c > 6.5% received treatment with nateglinide or glyburide: • Nateglinide produced significant increases in mean HbA1c and mean fasting plasma glucose, compared to glyburide.
Nateglinide 120mg TID vs. Glyburide 10mg QD[62]	n=152	8 week randomized, double-bind, placebo controlled trial	In comparing the effects of nateglinide, glyburide and placebo on postmeal glucose excursions and insulin secretion in previously diet-treated patients with type 2 diabetes: • During the liquid meal challenge, nateglinide reduced the incremental glucose area under the curve more effectively than glyburide (P<0.05). • Glyburide reduced fasting plasma glucose levels more effectively than Starlix (P<0.001). • C-peptide induced by glyburide was greater than that induced by Starlix (P<0.01). • During the solid meal challenges, nateglinide and glyburide elicited similar overall glucose control, however, the insulin AUC induced by nateglinide was significantly less than that induced by glyburide (P=0.01).
Nateglinide + Metformin vs. Repaglinide + Metformin[63]	n=192	16 week open label, parallel-group, randomized, multicenter trial	This study was conducted to compare efficacy and safety of repaglinide and nateglinide used in combination with metformin in type 2 diabetics: • Final HbA1c values were lower for the repaglinide/metformin group versus treatment with nateglinide/metformin (7.1% vs. 7.5%) • Repaglinide/metformin showed significantly greater mean reductions in HbA1c (P<0.001) and of fasting plasma glucose (P=0.002). • Self-monitoring of blood glucose profiles were significantly lower for the repaglinide/metformin combination before breakfast, before lunch,

			and at 2:00AM. • Changes in the area under the curve of postprandial glucose, insulin, or glucagons peaks after a test meal were not significantly different for the two treatment groups during the study. • Safety assessments were comparable for the 2 assessments.
Nateglinide alone and in combination with Metformin[64]	n=701	24 week randomized, double-blind study	Patients among 4 treatment groups (nateglinide alone, metformin alone, the combination, and placebo) were evaluated as to the efficacy and tolerability of the treatments: • HbA1c was reduced from baseline with nateglinide and metformin, but was increased with placebo (P< or = 0.0001). • Changes in fasting plasma glucose followed the same pattern (-0.7, -1.6, and +0.4mmol/l, P< or = 0.0001). • Combination therapy was additive compared to monotherapy (P< or = 0.01). • After sustacal challenge, there was greater reduction in mealtime glucose with nateglinide monotherapy compared to metformin monotherapy or placebo (P< or = 0.0001). • All regimens were well tolerated.
Rosiglitazone + Placebo vs. nateglinide + rosiglitazone[65]	n=402	24 week multicenter, double-blind, randomized study	In evaluating the effects of nateglinide added to rosiglitazone monotherapy on glycemic control and on postprandial glucose and insulin levels in patients with type 2 diabetes: • Target HbA1c was achieved by 38% of patients treated with combination therapy and 9% of patients remaining on rosiglitazone monotherapy. • In the nateglinide treated group, fasting plasma glucose levels decreased by 0.7mmol/l, 2-hour postprandial glucose levels decreased by 2.7mmol/l, and 30-minute insulin levels increased by 165mmol/l compared with no changes from baseline in the placebo plus rosiglitazone group.
Repaglinide vs. glimepiride[66]	n=124	12 month, randomized, placebo-controlled, double-blind trial	In comparing repaglinide and glimepiride with regard to glycemic control and parameters known to be cardiovascular risk factors: • After 6 and 12 months of treatment, fasting plasma glucose levels and HbA1c values were significantly reduced from baseline in both groups (P<0.01). • After 6 months, postprandial glucose levels were significantly decreased only in the repaglinide group (P<0.05), however, at 12 months, postprandial glucose levels were significantly reduced from baseline in both groups (P<0.01 for repaglinide and P<0.05 for glimepiride). • No significant changes in baseline fasting plasma insulin or postprandial plasma insulin levels were seen in either group at 6 months, although levels were significantly increased in the repaglinide group at 12 months (P<0.05). • Repaglinide significantly lowered levels of lipoprotein (a), plasminogen activator inhibitor-1, and homocysteine (P<0.05 vs. baseline). • Amaryl significantly lowered levels of lipoprotein (a) and homocysteine at 6 months (both P<0.01) and all three cardiovascular parameters were lowered after 12 months.
Repaglinide vs. Metformin[67]	n=112	12 month open, uncontrolled, randomized study	In an evaluation of glycemic control and cardiovascular risk profiles of patients with type 2 diabetes following treatment with repaglinide or metformin: • A decrease in postprandial plasma glucose was significantly greater in the repaglinide group (P<0.05). • During the treatment period, fasting plasma insulin decreased significantly in both groups, but more so with metformin (P<0.05). • 2-hour postprandial plasma insulin levels decreased only in the metformin group (P<0.05). • Significant improvements between baseline and final visit were demonstrated in one or both groups in the following cardiovascular risk factors: total cholesterol, LDL cholesterol, triglycerides, plasminogen activator inhibitor, lipoprotein (a), and homocysteine.

Additional Evidence

Dose Simplification: Not Applicable.

Stable Therapy: When transferring from most other antidiabetic agents to repaglinide, a transition period generally is not required. Administration of the other oral antidiabetic agent may be abruptly discontinued and repaglinide initiated the day after the final dose of the other oral agent. Close monitoring is important for one week or longer after switching to repaglinide. Since the agents in this class are both administered three times daily, there is not a dosing advantage of switching from one agent to the other.

Data is limited concerning use of these drugs as monotherapy in patients who did not achieve adequate glycemic control with other oral antidiabetic monotherapy (metformin and glyburide). In studies of patients who had previously received oral antidiabetic therapy, the difference in HbA1c between repaglinide and placebo was 1.6%-1.7%, reflecting mainly an increase in HbA1c in the placebo group.[3] Another study in patients on metformin, switching to repaglinide did not appreciably improve glycemic control; however, repaglinide monotherapy maintained glycemic control with fewer GI adverse events than metformin monotherapy. Changing from other oral antidiabetic agents to repaglinide did not influence body weight.

Data from a substudy of the UKPDS in newly diagnosed type 2 diabetics receiving intensive therapy showed that secondary failure with repaglinide occurred overall at about 7% per year. The failure rate at 6 years was 48% among patients receiving glyburide and about 40% among patients receiving chlorpropamide.[3] In another UKPDS substudy, progressive deterioration in diabetes control was such that repaglinide monotherapy was effective in only about 50% of patients after 3 years.

Impact on Physician Visits: Two modeled US studies projected lifetime medical utilization and outcomes for patients with type 2 diabetes.[68] Repaglinide plus rosiglitazone was dominant over rosiglitazone in one analysis and repaglinide plus metformin was dominant over nateglinide plus metformin in the other. A Canadian study showed similar results in patients who switched from a sulfonylurea to repaglinide versus those who remained on a sulfonylurea.

VII. Conclusions

Postprandial hyperglycemia has been associated with an increased risk of microvascular and macrovascular diabetic complications. Repaglinide and nateglinide target postprandial hyperglycemia, however, their long-term benefit on diabetic complications is unknown. Although both drugs have similar mechanisms of action, nateglinide appears to have a quicker onset of action and slightly shorter duration of action than repaglinide. This may explain the difference in the incidence of hypoglycemia with nateglinide (2.4%) and repaglinide (31%). The incidence of hypoglycemia with the meglitinides still tends to be lower than with sulfonylureas. Head- to- head studies are needed to fully evaluate this difference, but due to repaglinide's longer duration of action, it will likely have a higher incidence of hypoglycemia. Clinically, repaglinide and nateglinide offer similar effectiveness, with repaglinide showing greater benefit in combination with metformin. Repaglinide also has more extensive labeling as it is indicated for use in combination with the thiazolidinediones.

There are advantages and disadvantages with each drug in this class. Due to a lack of direct clinical comparison studies with nateglinide and repaglinide, all brand products within the meglitinide class are comparable to each other and offer no significant clinical advantage over other alternatives in general use.

VIII. Recommendations

No brand meglitinide is recommended for preferred status.

Sulfonylureas (AHFS 682020) Single Entity Agents

I. Comparative Indications for the Sulfonylureas

Sulfonylurea drugs are derivatives of sulfonamides and are divided into 2 groups: First generation and second generation. The sulfonylurea drugs are used as adjuncts to diet and exercise in the treatment of type 2 diabetes. The mechanism of action of the sulfonylureas results from binding of the drugs to the plasma membrane of functional beta-cells in the pancreatic islets, thereby causing a decrease in potassium (K+) permeability and membrane depolarization.[24] When depolarization occurs, there is an increase in intracellular calcium ions and subsequent exocytosis in insulin-containing secretory granules. The sulfonylureas increase insulin secretion at stimulatory levels lower than that required for glucose, suggesting that they enhance beta-cell response rather than change beta-cell sensitivity to glucose.

There are four first-generation sulfonylureas, all of which have generic alternatives. In comparison, there are five second-generation drugs, which also offer generic alternatives. Table 1 lists the products in this class and Table 2 compares their indications. This review encompasses all dosage forms and strengths.

Table 1. Sulfonylurea Products in this Review

Generation	Generic Name	Formulation	Example Brand Name (s)
First	Acetohexamide	Oral	Acetohexamide*
	Chlorpropamide	Oral	Diabinese*
	Tolazamide	Oral	Tolinase*
	Tolbutamide	Oral	Tolbutamide*
Second	Glimepiride	Oral	Amaryl
	Glipizide Glipizide ER	Oral Oral Extended-Release	Glucotrol* Glucotrol XL*
	Glyburide	Oral	DiaBeta, Micronase*
	Micronized Glyburide	Oral	Glycron*, Glynase PresTab*

*Generic Available

Table 2. FDA-Approved Indications for the Sulfonylureas[3, 47]

	Type 2 diabetes Monotherapy	Combination Therapy in Type 2 Diabetes
Acetohexamide	✓	✓
Chlorpropamide (Diabinese)	✓	✓
Tolazamide (Tolinase)	✓	✓
Tolbutamide	✓	✓
Glimepiride (Amaryl)	✓	✓
Glipizide (Glucotrol)	✓	✓
Glipizide ER (Glucotrol XL)	✓	✓
Glyburide (DiaBeta)	✓	✓
Glyburide (Micronase)	✓	✓
Micronized Glyburide (Glycron)	✓	✓
Micronized Glyburide (Glynase PresTab)	✓	✓

II. Pharmacokinetic Parameters

The sulfonylurea drugs have similar mechanisms of action and hypoglycemic effect, but the first and second generation drugs differ in that the second generation drugs possess a more nonpolar or lipophilic side chain.[24] As a result, second generation drugs have a higher intrinsic potency and require lower effective doses and serum concentrations.

Absorption
Sulfonylurea drugs are well absorbed after oral administration. All drugs in this class can be taken with food except for glipizide. Glipizide absorption is delayed with taken with food. Tolbutamide, glyburide, and glipizide are more effective when taken 30 minutes before a meal. Tolazamide is absorbed much more slowly than the other sulfonylureas.

Distribution, Metabolism and Elimination
Sulfonylureas are metabolized in the liver to active and inactive metabolites and are excreted primarily in the urine. Patients with severe liver disease may experienced prolonged hypoglycemic effects due to decreased metabolism. All sulfonylureas are strongly bound to plasma proteins, primarily albumin. Protein binding of the first-generation drugs is ionic, whereas that of the second-generation agents is nonionic. The clinical significance of this is unknown, however, because the sulfonylurea drugs are bound to albumin by ionic bindings, first generation agents may be more likely to be displaced by drugs that compete for binding to proteins.

Pharmacokinetic properties among the sulfonylureas differ in the duration of hypoglycemic effects. Tolbutamide is short-acting due to rapid metabolism to an inactive metabolite, and may be most useful in patients with kidney disease. The duration of acetohexamide may be prolonged in renal disease because the drug's active metabolite is 2.5 times as potent as the parent compound. Renal elimination of chlorpropamide may be sensitive to changes in urinary pH; when the urinary pH is <6, urinary excretion decreases and hepatic metabolism serves as the primary route of elimination. Table 3 compares the pharmacokinetic profiles of the sulfonylurea agents.

Table 3. Pharmacokinetic Parameters of the Sulfonylureas[24]

	Serum $t_{1/2}$	Onset (hrs)	Duration (hrs)	Renal Excretion (%)	Active metabolites
Acetohexamide	6-8	1	12-24	100	Yes
Chlorpropamide	36	1	24-60	100	Yes
Tolazamide	7	4-6	12-24	100	Yes
Tolbutamide	4.5-6.5	1	6-12	100	No
Glipizide	2-4	1-3	10-24	80-85	No
Glipizide ER	2-5	2-3	24	80	No
Glyburide	10	2-4	16-24	50	Yes
Glyburide micronized	4	1	12-24	50	Yes[1]
Glimepiride	9	2-3	24	60	Yes

[1] Weakly Active

III. Drug Interactions

Drug interactions with the sulfonylureas occur with the class as a whole. There are no interactions among the sulfonylurea agents that would make one agent superior to another. Although there are few documented level 1 (rapid onset, major severity) interactions with drugs in this class, there are several level 2 interactions present with the sulfonylureas. The hypoglycemic affect of sulfonylureas may be enhanced due to decreased hepatic metabolism, inhibition of renal excretion, displacement from protein-binding sites (NSAIDs and azoles), decreased blood glucose, and alteration of carbohydrate metabolism. In contrast, the hypoglycemic effects may be decreased when there is a increase in hepatic metabolism, a decrease in insulin release, and an increased renal excretion. Table 4 lists the level 2 interactions with the sulfonylureas.

Other documented, but less severe interactions occur with the following drugs or classes of drugs: clofibrate, fenfluramine, urinary acidifiers, androgens, cholestyramine, cyclosporine, digoxin, fluvoxamine, gemfibrozil, H-2 blockers, macrolide antibiotics, omeprazole, probenecid, quinolones (ciprofloxacin), and tricyclic antidepressants.

Table 4. Clinically Significant Drug Interactions [23]

Significance	Interaction	Mechanism
1 Delayed, Major, Suspected	Glyburide and Tracleer	Tracleer may increase the metabolism (CYP2C9 and CYP3A4) of glyburide. Other mechanisms may also be involved. Plasma levels of Tracleer and glyburide may be decreased. Increased risk of elevated liver enzymes, resulting in serious liver injury may occur.
2 Delayed, Moderate, Probable	Sulfonylureas and anticoagulants	Metabolic degradation of sulfonylureas is slowed by oral anticoagulants, leading to accumulation of sulfonylurea and possible clinical hypoglycemia.
2 Delayed, Moderate, Suspected	Sulfonylureas and chloramphenicol	Chloramphenicol reduces sulfonylurea hepatic clearance leading to accumulation of the sulfonylurea and potentially hypoglycemia.
2 Delayed, Moderate, Probable	Sulfonylureas and Diazoxide	Two proposed mechanisms: decreased insulin release secondary to diazoxides effect on cell membrane calcium flux or stimulation of alpha-adrenergic receptor sites in the beta cell and diazoxide stimulation of the release of catecholamines, which results in increased glucose and free fatty acids. Result could cause hyperglycemia.
2 Rapid, Moderate, Established	Sulfonylureas and Ethanol	Ethanol prolongs glipizide activity by delaying glipizide absorption and elimination. Chronic use of ethanol may cause a decrease in the half-life of tolbutamide by causing a decrease in absorption of the active drug and a more rapid metabolism by the liver. Ethanol ingestion in patients taking chlorpropamide may result in a disulfiram-like reaction.
2 Delayed, Moderate, Suspected	Sulfonylureas and Fluconazole (Azole antifungals)	Fluconazole inhibits sulfonylurea metabolism, causing the hypoglycemic effects of sulfonylureas to be increased.
2 Rapid, Moderate, Suspected	Sulfonylureas and MAO inhibitors	Mechanism is unknown. MAO inhibitors enhance the hypoglycemic actions of sulfonylureas.
2 Delayed, Moderate, Established	Sulfonylureas and Phenylbutazones	Mechanism varies: interference in renal excretion, displacement from protein binding sites, and delayed metabolism of the sulfonylurea. The end effect is enhanced hypoglycemic effects.
2 Delayed, Moderate, Probable	Sulfonylureas and Rifamycins	The rifamycins may increase the hepatic metabolism of sulfonylureas. The serum and $t_{1/2}$ levels of sulfonylureas may be decreased while increasing the clearance , possibly resulting in hyperglycemia.
2 Delayed, Moderate Probably	Sulfonylureas and Salicylates	Salicylates reduce plasma glucose levels and enhance insulin secretion. Inhibition of prostaglandin synthesis may inhibit acute insulin responses to glucose. Displaced sulfonylurea binding has also been suggested, all leading to an increased hypoglycemic effect.
2 Delayed, Moderate, Suspected	Sulfonylureas (tolbutamide) and Sulfinpyrazone	Sulfinpyrazone impairs the hepatic metabolic conversion of Tolbutamide, causing decreased clearance and increased half-life of tolbutamide, and hypoglycemia.
2 Delayed, Moderate, Suspected	Sulfonylureas and Sulfonamides	Sulfonamides may impair hepatic metabolism of sulfonylureas or alter plasma protein binding, resulting in an increase in the half-life of the sulfonylurea, and hypoglycemia.
2 Delayed, Moderate, Probable	Sulfonylureas and Thiazide Diuretics	Thiazide diuretics may decrease insulin tissue sensitivity, decrease insulin secretion or increase potassium loss, causing hyperglycemia.
2 Delayed, Moderate, Suspected	Sulfonylureas (chlorpropamide) and Urinary Alkalinizers	The renal clearance of chlorpropamide increases as urinary pH increases. Alkalinization of the urine by an agent such as sodium bicarbonate may increase the elimination of chlorpropamide.

IV. Adverse Drug Events of the First and Second Generation Sulfonylureas

Gastrointestinal disturbances are the most common adverse drug events with the sulfonylureas. In most products, GI effects appear to be dose related and may subside with dose reduction. There are no significant differences in the rate of adverse drug events with the sulfonylureas. One study compared the clinical characteristics and time course of hypoglycemia between glimepiride (Amaryl) and glyburide and showed that there were no essential differences in the clinical characteristics and time course between the two drugs.[69] Tables 5 and 6 compare the reported adverse events for the first and second-generation sulfonylureas.

Table 5. Common Adverse Events (%), by System, Reported for the First-Generation Sulfonylureas

Adverse Event	Acetohexamide	Chlorpropamide	Tolazamide	Tolbutamide
Metabolic				
Hypoglycemia	✔	✔	✔	✔
Disulfiram Like Rxn	N/A	✔	N/A	N/A
Hepatic Porphyria	N/A	✔	N/A	N/A
Jaundice	✔	✔	✔	✔
Gastrointestinal				
Nausea	✔	<5	✔	✔
Diarrhea	✔	<2	✔	N/A
Vomiting	✔	<2	✔	N/A
Anorexia	N/A	<2	✔	N/A
Hunger	N/A	<2	N/A	N/A
Skin and Appendages				
Pruritis	✔	<3	✔	✔
Urticaria	✔	<1	✔	✔
Macropapular eruptions	✔	<1	N/A	✔
Photosensitivity Rxn	✔	✔	✔	✔
Other				
Proctocolitis	N/A	<1	N/A	N/A
Headache	✔	N/A	✔	✔
Weight Gain	✔	N/A	✔	✔

N/A Incidence not available **✔ Adverse event reported; specific percentages not available**

Table 6. Common Adverse Events (%), by System, Reported for the Second-Generation Sulfonylureas

Adverse Event	Glimepiride	Glipizide	Glipizide ER	Glyburide	Micronase, Glycron, Glynase
Metabolic					
Hypoglycemia	0.9-1.7	✔	3.4	✔	✔
Disulfiram Like Rxn	N/A	✔	N/A	✔	N/A
Hepatic Porphyria	N/A	N/A	N/A	✔	✔
Jaundice	✔	✔	N/A	✔	✔
Gastrointestinal					
Nausea	>1	✔	<3	1.8	1-2
Diarrhea	<1	✔	5.4 (0)	N/A	N/A
Vomiting	<1	N/A	<3	N/A	N/A
Anorexia	N/A	N/A	<1	N/A	N/A
Hunger	N/A	N/A	N/A	N/A	N/A
Skin and Appendages					
Pruritis	<1	✔	<3	1.5	1.5
Urticaria	<1	✔	<1	1.5	1.5
Macropapular eruptions	N/A	✔	N/A	1.5	N/A
Photosensitivity Rxn	✔	✔	N/A	✔	✔
Other					
Proctocolitis	N/A	N/A	N/A	N/A	N/A
Headache	>1	✔	8.6 (8.7)	N/A	N/A
Weight Gain	N/A	N/A	N/A	N/A	N/A
Tremor	N/A	N/A	3.6 (0)	N/A	N/A
Asthenia	>1	N/A	10.1 (13)	N/A	N/A

N/A Incidence not available **✔ Adverse event reported; specific percentages not available**
Incidence in placebo listed in parenthesis when available

V. Dosing and Administration

As with all oral antidiabetic medications, dosing is variable and should be individualized according to the severity of the disease. All of the sulfonylureas (except tolbutamide) can be dosed once daily in smaller doses, with larger doses given in 2-3 divided doses daily. Therefore, there are no significant advantages in dosing with one drug over another product in the sulfonylurea class.

Table 7. Dosing for the Sulfonylureas[3, 24]

Agent	Availability	Dose /Frequency/Duration
Acetohexamide	250mg and 500mg Tablets	Starting: 250mg QD before breakfast Titration: Increments of 250-500mg QD at 5-7 day intervals, Doses of <1g can be given as a single daily dose Maximum: 1.5g QD
Diabinese®	100mg and 250mg Tablets	Starting: 250mg QD with breakfast (100-125mg QD for geriatric patients) Titration: Increments of 50-125mg QD at 3-5 day intervals, If GI intolerance occurs, daily dose can be divided in 2 doses Usual maintenance dose: 250mg QD Maximum: 750mg QD
Chlorpropamide	100mg and 250mg Tablets	Starting: 250mg QD with breakfast (100-125mg QD for geriatric patients) Titration: Increments of 50-125mg QD at 3-5 day intervals, If GI intolerance occurs, daily dose can be divided in 2 doses Usual maintenance dose: 250mg QD Maximum: 750mg QD
Tolinase®	100mg, 250mg, 500mg Tablets	Starting: 100mg-250mg QD with breakfast (100mg for geriatric patients) Titration: Increments of 100mg-250mg weekly intervals Doses >500mg QD should be given in 2 daily doses. Usual maintenance dose: 250mg-500mg QD Maximum: 1000mg QD
Tolazamide	100mg, 250mg, 500mg Tablets	Starting: 100mg-250mg QD with breakfast (100mg for geriatric patients) Titration: Increments of 100mg-250mg weekly intervals Doses >500mg QD should be given in 2 daily doses. Usual maintenance dose: 250mg-500mg QD Maximum: 1000mg QD
Tolbutamide	500mg Tablet	Starting: 1000-2000mg QD, given in divided doses after meals Maintenance: >2000mg are seldom required Maximum: 3000mg QD
Amaryl®	1, 2, and 4mg Tablets	Starting: 1-2mg QD with breakfast (1mg QD in geriatric patients) Titration: Increments of 1-2mg every 1-2weeks Maintenance: 1-4mg QD Maximum: 8mg QD Note: Dosing in children <16 has not been established.
Glucotrol®	5mg and 10mg Tablets	Starting: 5mg QD 30 min. before breakfast (2.5mg in geriatric patients) 5mg-10mg QD in pts. transfd. from other antidiabetic agents Titration: Increments of 2.5-5mg QD every 3-7 days Maintenance: 2.5mg-40mg QD or in divided doses Maximum: 40mg QD Note: When switching from conventional to extended-release tablets, the nearest equivalent total daily dose should be given once daily. Doses of conventional glipizide > 15mg should be divided according to patient mealtimes and response.
Glipizide	5mg and 10mg Tablets	Starting: 5mg QD 30 min. before breakfast (2.5mg in geriatric patients) 5mg-10mg QD in pts. transfd. from other antidiabetic agents Titration: Increments of 2.5-5mg QD every 3-7 days Maintenance: 2.5mg-40mg QD or in divided doses

		Maximum: 40mg QD Note: When switching from conventional to extended-release tablets, the nearest equivalent total daily dose should be given once daily. Doses of conventional glipizide > 15mg should be divided according to patient mealtimes and response.
Glucotrol XL®	2.5mg, 5mg, and 10mg Tablets	Starting: 5mg QD with breakfast Titration: 3 month intervals Maintenance: 5mg-10mg QD Maximum: 20mg QD Note: Tablets should be swallowed whole and should not be divided. The extended-release tablet is designed to remain intact, slowly releasing the drug; patients may notice a tablet-like substance in their stool.
Glipizide ER	2.5mg, 5mg, and 10mg Tablets	Starting: 5mg QD with breakfast Titration: 3 month intervals Maintenance: 5mg-10mg QD Maximum: 20mg QD Note: Tablets should be swallowed whole and should not be divided. The extended-release tablet is designed to remain intact, slowly releasing the drug; patients may notice a tablet-like substance in their stool.
DiaBeta®	1.25mg, 2.5mg, and 5mg	Starting: 2.5mg-5mg QD 30 min. before breakfast (1.25mg in geriatric patients) Titration: Increments of 2.5mg at weekly intervals Maintenance: 1.25mg -20mg Doses >10mg may have a better response when divided in 2 daily doses Maximum: 20mg QD
Micronase®	1.25mg, 2.5mg, and 5mg	Starting: 2.5mg-5mg QD 30 min. before breakfast (1.25mg in geriatric patients) Titration: Increments of 2.5mg at weekly intervals Maintenance: 1.25mg -20mg Doses >10mg may have a better response when divided in 2 daily doses Maximum: 20mg QD
Glyburide	1.25mg, 2.5mg, and 5mg	Starting: 2.5mg-5mg QD 30 min. before breakfast (1.25mg in geriatric patients) Titration: Increments of 2.5mg at weekly intervals Maintenance: 1.25mg -20mg Doses >10mg may have a better response when divided in 2 daily doses Maximum: 20mg QD
Glycron®	1.5mg, 3mg, 4.5mg, and 6mg	Starting: 1.5mg-3mg QD with breakfast (0.75 mg in geriatric patients) Titration: Increments of <1.5mg at weekly intervals Maintenance: 0.75mg –12mg QD Maximum: 12mg QD Doses > 6mg QD may have a better response when divided in 2 daily doses Note: Micronized formulations of glyburide are not bioequivalent with conventional formulations.
Glynase® PresTab	1.5mg, 3mg, and 6mg	Starting: 1.5mg-3mg QD with breakfast (0.75 mg in geriatric patients) Titration: Increments of <1.5mg at weekly intervals Maintenance: 0.75mg –12mg QD Maximum: 12mg QD Doses > 6mg QD may have a better response when divided in 2 daily doses Note: Micronized formulations of glyburide are not bioequivalent with conventional formulations.
Glyburide Micronized	1.5mg, 3mg, 4.5mg, and 6mg	Starting: 1.5mg-3mg QD with breakfast (0.75 mg in geriatric patients) Titration: Increments of <1.5mg at weekly intervals Maintenance: 0.75mg –12mg QD Maximum: 12mg QD Doses > 6mg QD may have a better response when divided in 2 daily doses Note: Micronized formulations of glyburide are not bioequivalent with conventional formulations.

Special Dosing Considerations

- In general, initial doses of sulfonylureas in patients with renal or hepatic disease should be more conservative to avoid hypoglycemic reactions.
- Pregnancy category has not been established with all sulfonylureas, but has been designated a pregnancy category C with the following drugs: acetohexamide, glimepiride, glyburide, glipizide, and tolazamide.
- According to Aventis, formal studies have not evaluated glimepiride (Amaryl) when the tablet has been broken or crushed, and therefore, they do not recommend administration of the tablet in any form other than the intact tablet.
- Generally, the immediate-release sulfonylurea agents can be crushed for alternative dosing when needed.

VI. Comparative Effectiveness of the Sulfonylureas

The sulfonylurea drugs have been available for many years. They have been used and studied in combination with insulin and other oral hypoglycemic agents. Table 8 lists a few current comparative studies of drugs within the class.

Table 8. Additional Outcomes Evidence for the Sulfonylureas

Study	Sample	Duration	Results
Glimepiride vs. glyburide[70]	n=520	12 month multicenter retrolective	In comparing the effects of glimepiride or glyburide on body weight in patients with type 2 diabetes: • Mean weight loss and reduction in body mass index from baseline were greater with glimepiride than with glyburide (P<0.001). • Both glimepiride and glyburide led to decreases in fasting blood glucose (-2.43+/-0.24mmol/l vs. –3.03+/-0.24mmol/l; P<0.001 vs. baseline). • Both treatments were associated with a decrease in serum total cholesterol and LDL cholesterol. • Triglycerides were lower in the glyburide group and HDL cholesterol was higher in the glimepiride group only.
Glimepiride vs. glipizide as add-on therapy with metformin[71]	-	12 week randomized, double-blind, crossover study	When looking at the metabolic and vascular effects of glimepiride and glipizide during administration with metformin: • Glycemic responses for glimepiride and glipizide were similar and there were no differences in augmentation index during treatment. • There was also no difference in both treatments in presser responsiveness or coetaneous microvascular vasodilator responses.
glyburide vs. glipizide[72]	n=18	15 month period	Comparative evaluation of glyburide and glipizide looking at efficacy and potency showed: • Similar doses of glipizide or glyburide resulted in comparable reduction in fasting plasma glucose, HbA1c, and increase in first phase insulin response intravenous glucose tolerance testing. • There was a greater reduction in fasting plasma glucose and 2 hour postprandial plasma glucose with glipizide than with glyburide at 6 months.
2nd generation Sulfonylureas after failure to 1st generation agents [73]	n=55	6 months	When treated with either glyburide or glipizide in type 2 diabetics with previous failure to a first generation agent: • No significant changes in metabolic values (fasting plasma glucose) were seen with the initiation of either glyburide or glipizide therapy. • Lipid profiles were not significantly altered with either of the treatments. • Fasting plasma glucose and HbA1c were 200 +/- 27 mg/dL and 11.9 +/- 2.0%, respectively, during treatment with first-generation drugs and did not change significantly following therapy with the second-generation agents (fasting plasma glucose, 205 +/- 20 mg/dL; HbA1c, 11.2 +/- 1.2%). P > 0.60 for all comparisons.
Glipizide vs. glyburide[74]	n=46	15 months	In evaluating the long-term effects of glycemic control and insulin secretion between glipizide and glyburide: • A comparable reduction in HbA1c was seen by both agents versus placebo.

			• Glipizide and glyburide maintained lowered postprandial glucose levels and increased fasting and postprandial insulin levels compared to placebo.
Extended-release GITS vs. immediate-release glipizide[75]	-	5 day pharmacokinetic and pharmacodynamic study	When reviewing the differences between the extended-release glipizide GITS formulation compared to that of immediate-release glipizide: • Mean C_{max} after immediate-release glipizide was significantly greater than after glipizide GITS, and the t_{max} was considerably shorter. • The mean C_{min} with glipizide GITS was about 80% higher than with immediate-release glipizide, the mean AUC0-24 was significantly lower. • Despite the lower plasma concentrations with glipizide GITS in this short-term study, the two formulations had similar effects on serum concentrations of glucose, insulin, and C-peptide. • The absence of a pronounced peak plasma concentration with the GITS formulation might confer advantages in terms of maintaining clinical effectiveness and reducing the potential to cause adverse effects.

Additional Evidence

Dose Simplification: Differences in adherence and persistence with therapy of once-daily dosing compared with twice-daily dosing of glipizide, were evaluated in patients with type 2 diabetes.[76] Adherence rates were 60.5% in the once-daily group compared to 52.0% in the twice-daily group. At 12 months, rates of persistence were 44.4% in the once-daily group and 35.8% in the twice-daily group. This was an adherence study only, based on evaluation of pharmacy benefit manager claims data. The study did not measure the impact of adherence on HbA1c.

Stable Therapy: When transitioning from most sulfonylurea agents to another sulfonylurea, a transition period generally is not required, and administration of the sulfonylurea agent may be discontinued abruptly.[3] Patients should be monitored closely for hypoglycemia after transitioning from one agent to another.

Ten-year data from UKPDS in patients who received initial therapy with conventional antidiabetic treatment or intensive regimens indicate that intensive treatment with monotherapy generally is not capable of maintaining strict glycemic control over time and that combination therapy becomes necessary in most patients to reach target glycemic levels.[3]

Secondary failure to sulfonylurea drugs can occur with progressively decreasing diabetic control following 1 month to several years of good control.[3] A substudy group of UKPDS showed that secondary failure occurred overall at about 7% per year. The failure rate at 6 years was 48% among patients receiving glyburide and about 40% among patients receiving chlorpropamide. In another study, monotherapy with a sulfonylurea was effective in only about 50% of patients after 3 years and in about 25% of patients after 9 years.

Impact on Physician Visits: While no peer reviewed studies (in Medline/Pubmed or Ovid) formally evaluated the impact of sulfonylureas and physician visits, one study by Kaiser Permanente found that 38% of type 2 diabetic patients were not tested for HbA1c and of this group, 32% failed to visit a primary care physician for treatment.[77] The study found that 5-10% of persons with type 2 diabetes avoid contact with the medical care system.

VII. Conclusions

First-generation sulfonylurea drugs are used less commonly today than the second generation drugs. Data presented in this review shows there are no clinical differences with regard to indications, drug-interactions, adverse events, or clinical effectiveness patterns with the drugs in this class. There are also multiple generic products available in this class. Therefore, all brand products within the class reviewed are comparable to each other and to the generics in the sulfonylurea class and offer no significant advantage over other alternatives in general use.

VIII. Recommendations

No brand sulfonylurea is recommended for preferred status.

Thiazolidinediones (AHFS 682028) Single Entity Agents

I. Comparative Indications for the Thiazolidinediones

The thiazolidinediones improve glycemic control by improving insulin sensitivity, therefore, depending on the presence of insulin for their mechanism of action. Studies indicate the thiazolidinediones improve insulin sensitivity in muscle and adipose tissue and inhibit hepatic gluconeogenesis.[24] They are highly selective and potent agonists for the peroxisome proliferators-activated receptor-gamma (PPAR) that are found in adipose tissue, skeletal muscle, and the liver. Activation of PPAR regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization of fatty acid metabolism.

There are two thiazolidinedione products available. Table 1 lists the brand and generic names of the products in this class, while Table 2 compares their FDA approved indications. Combination products are reviewed in a separate section at the end of this document. This review encompasses all dosage forms and strengths.

Table 1. Thiazolidinedione Products in this Review

Generic Name*	Formulation	Example Brand Name
Pioglitazone	Oral	Actos
Rosiglitazone	Oral	Avandia

*There are no generic formulations available for any of the medications in this class.

The thiazolidinediones are indicated as pharmacological agents to treat type 2 diabetes mellitus, as an adjunct to diet and exercise. Both drugs are indicated and have been studied extensively in combination with other antidiabetic treatments. The thiazolidinediones are not recommended in patients with New York heat Association Class III or IV heart failure (See adverse events)

Table 2. FDA-Approved Indications for the Thiazolidinediones[3, 47]

	Monotherapy in Type 2 Diabetes Mellitus	Combination Therapy with sulfonylureas, metformin, or insulin in Type 2 Diabetes Mellitus	Addition to fixed combination of glyburide and metformin	Addition with Prandin when diet, exercise and monotherapy with another oral hypoglycemic agent is unsuccessful
Pioglitazone (Actos)	✓	✓	✓	✓
Rosiglitazone (Avandia)	✓	✓	✓	✓

II. Pharmacokinetic Parameters

Absorption
Pioglitazone levels are first measurable about 30 minutes following oral absorption, with peak concentrations observed within 2 hours.[47] In comparison, peak plasma concentrations of rosiglitazone are observed at 1 hour after dosing.

Distribution, Metabolism and Elimination
Rosiglitazone is extensively metabolized and excreted in the urine. All circulating metabolites of rosiglitazone are considered less potent than the parent compound and do not contribute to the insulin-sensitizing activity of rosiglitazone. Pioglitazone is also extensively metabolized, with M-II, M-IV, and M-III being pharmacologically active.

Hepatic Impairment
Rosiglitazone clearance was significantly lower in moderate to severe liver disease patients compared with healthy subjects. This results in an increased C_{max} by 2-fold, an AUC by 3-fold, and a longer elimination half-life by 2 hours. When compared to healthy subjects, patients taking pioglitazone with impaired hepatic function had approximately 45% reduction in pioglitazone and total pioglitazone mean peak concentrations but no change in the mean AUC values. Both drugs should not be initiated in patients with clinical evidence of active liver disease or increased serum transaminase levels (ALT more than 2.5 times the upper limit o f normal). Table 3 differentiates between the important pharmacokinetic parameters of the two drugs.

Table 3. Pharmacokinetic Parameters[24]

	T_{max} (hr)	Food Effect	Volume of Distribution	Protein Binding (%)	Metabolism Mechanism	Excretion (hr)	Elimination Half-Life
Pioglitazone	2[2] 3-4[3]	Delays time to peak concentration; does not alter extent of absorption	0.63L/kg	>99	Hydroxylation, oxidation, CYP2C8, CYP3A4, CYP1A1	Urine (15-30%)	3-7
Rosiglitazone	1	28% decrease in C_{max} and delay in T_{max} (1.75 hr); no overall change in AUC	17.6L	99.8	N-demethylation, hydroxylation, conjugation, CYP2C8, CYP2C9 (minor)	Urine (64%), feces (23%)	3-4 hours

[2]In the fasting state.
[3]In the fed state.

III. Drug Interactions with the Thiazolidinediones

In vitro drug metabolism studies indicate that rosiglitazone does not inhibit any of the major P450 enzymes at clinically relevant concentrations. Rosiglitazone was also shown to have no clinically relevant effect when given with the following drugs: nifedipine, oral contraceptives, glyburide, metformin, acarbose, digoxin, warfarin, ethanol, and ranitidine.[47]

In vivo drug interaction studies have suggested that pioglitazone may be a weak inducer of CYP450 isoform 3A4 substrate.[23, 47] Important 3A4 substrates are listed in Table 4, however, formal pharmacokinetic studies have not evaluated the effects of administration of Actos with all of the drugs listed.

Table 4. 3A4 Substrates*

Amlodipine	Nefazodone
Atorvastatin	Quinidine
Carbamazepine	Pravastatin
Cyclosporine	Rifampin
Diazepam	Ritonavir
Estrogens	Saquinavir
Ketoconazole	Sertraline
Lansoprazole	Tacrolimus
Midazolam	

*This table is not a complete listing of all of the 3A4 Substrates

In addition, ketoconazole appears to significantly inhibit the metabolism of pioglitazone. Glycemic control in patients on concomitant pioglitazone and ketoconazole should be monitored more frequently.
Pioglitazone has been formally studied with the following drugs where no significant clinical effect was seen in pharmacokinetic parameters with the associated drug: fexofenadine, glipizide, digoxin, warfarin, metformin, ranitidine, and theophylline.[47] Studies have documented drug interactions with midazolam (26% reduction in C_{max}), nifedipine ER, and atorvastatin calcium, when administered with pioglitazone. Table 5 lists another documented interaction of pioglitazone.

Administration of troglitazone (Rezulin), previously removed from the pharmaceutical market, was shown to reduce the plasma concentrations of both components of an oral contraceptive containing ethinyl estradiol and norethindrone by 30%, resulting in loss of contraception. Co-administration of pioglitazone and contraceptives has not been evaluated. However, rosiglitazone has been shown to have no clinically relevant effect on the pharmacokinetics or oral contraceptives, which are predominantly metabolized by CYP3A4. Until formally evaluated, additional caution should be exerted with use of pioglitazone and contraceptives.

Table 5. Clinically Significant Drug Interactions [23]

Significance	Interaction	Mechanism
4 Rapid, Moderate, Possible	Pioglitazone and Tequin (gatifloxacin)	Mechanism is unknown, however, a case of severe and persistent hypoglycemia has been documented. Gatifloxacin does not affect glucose tolerance or pancreatic beta-cell function.

IV. Adverse Drug Events

In clinical trials with pioglitazone and rosiglitazone, most adverse events were similar for monotherapy treated patients and for those treated with combination therapy. There was an increase in the occurrence of edema in patients treated with pioglitazone and insulin compared to insulin alone, resulting in weight gain, dyspnea, and requiring use of diuretics in 10 (n=379) patients.[47] Edema was not reported in the insulin plus placebo trial. Mild-moderate hypoglycemia was reported with pioglitazone in combination with insulin or sulfonylurea (1% for placebo, 2% for pioglitazone+Placebo, 8% for pioglitazone 15mg+insulin, and 15% for pioglitazone 30mg+insulin). Fewer than 0.12% of patients treated with pioglitazone in clinical trials were withdrawn due to abnormal lover function tests. In pre-approval trials, there were no cases if idiosyncratic drug reactions leading to hepatic failure.

Edema was reported in 4.8% of patients receiving rosiglitazone compared to 1.3% on placebo, 1.0% on sulfonylureas, and 2.2% on metformin.[47] Edema was reported with higher frequency in the rosiglitazone plus insulin trials (insulin 5.4%; combination 14.7%).[24] In pre-clinical trials of 4,598 patients treated with rosiglitazone, there was no evidence of drug-induced hepatotoxicity or elevated ALT levels. In controlled trials, 0.2% of patients treated with rosiglitazone had reversible elevations in Alt>3 times the upper limit of normal (ULN), compared to 0.2% on placebo. In pre-approval trials, there were no cases of idiosyncratic drug reactions leading to hepatic failure, however, in postmarketing surveillance, there have been reports of hepatic enzyme elevations 3 or more times the upper limit of normal and hepatitis. Monitoring of liver enzymes is recommended with use of both pioglitazone and rosiglitazone. Table 6 compares adverse events for pioglitazone and rosiglitazone.

Cardiovascular Warnings

Both pioglitazone and rosiglitazone have been associated with fluid accumulation and should be used with caution in patients with edema. The manufacturer labeling for these drugs notes that these agents can cause fluid retention when used alone or in combination with other antidiabetic agents (including insulin), which may lead to or exacerbate congestive heart failure. Use of these drugs in Class III or IV heart failure is not recommended. The following trials have further established this warning:

- In a 16 week study with pioglitazone, 2 of the 191 patients receiving pioglitazone 30mg QD plus insulin (1.1%) developed congestive heart failure compared to none of the 187 patients given insulin therapy alone. The study included patients with long-standing diabetes and a high rate of pre-existing medical conditions.[47] In postmarketing experience, cases of congestive heart failure have been reported in patients with and without previously known heart disease.
- In three 26 week trials in patients with type 2 diabetes, 215 patients received rosiglitazone 4mg plus insulin, 322 received 8mg rosiglitazone plus insulin, and 338 received insulin alone. These trials included patients with long-standing diabetes and a high prevalence of pre-existing conditions. An increased incidence of edema, cardiac failure, and other cardiovascular adverse effects was seen in patients on rosiglitazone plus insulin compared to insulin plus placebo.[47]

Table 6. Common Adverse Events (%), by System, Reported for the Thiazolidinediones [24, 47]

Adverse Event	Pioglitazone	Placebo	Rosiglitazone	Placebo
Body as a Whole				
Headache	9.1	6.9	5.9	5.0
Myalgia	5.4	2.7	N/A	N/A
Edema	4.8	1.2	4.8	1.3
Back Pain	N/A	N/A	4.0	3.8
Digestive System				
Diarrhea	N/A	N/A	2.3	3.3
Respiratory System				
URI	13.2	8.5	9.9	8.7
Sinusitis	6.3	4.6	3.2	4.5
Pharyngitis	5.1	0.8	N/A	N/A
Endocrine				
Hyperglycemia	N/A	N/A	3.9	5.7
Hypoglycemia	N/A	N/A	0.6	0.2
Hematological				
Anemia	N/A	N/A	1.9	0.7
ALT>3times ULN	0.26	0.25	0.2	0.2
Other				
Tooth disorder	5.3	2.3	N/A	N/A
Diabetes Aggravated	5.1	8.1	N/A	N/A
Fatigue	N/A	N/A	3.6	5.0
Injury	N/A	N/A	7.6	4.3

N/A Incidence not available

V. Dosing and Administration for the Thiazolidinediones

Dosing with the thiazolidinediones should be individualized. Dosage adjustments may be made at 8-12 weeks after the initiation of therapy, as determined by fasting plasma glucose. Both thiazolidinediones can be dosed once daily, although rosiglitazone has been shown (in monotherapy studies) to result in better reduction in fasting plasma glucose and HbA1c when given twice daily.[47] Neither drug has been studied in patients less than 18 years of age.

Table 7. Dosing for the Thiazolidinediones[3, 47]

	Availability	Dose /Frequency/Duration
Pioglitazone (Actos)	15mg, 30mg and 45mg Tablet	Starting: 15-30mg QD without regard to meals Maximum: 45mg QD No dose adjustments necessary in renal disease. Note: No data for use <18 years of age. No placebo-controlled clinical studies of more than 30mg QD have been studied with combination therapy.
Rosiglitazone (Avandia)	2mg, 4mg, and 8mg Tablet	Starting: 4mg QD or 2mg BID* without regard to meals Maximum: 8mg QD or 4mg BID No dosage adjustments necessary in renal disease. Note: No data for use <18 years of age. Doses >4mg in combination with insulin are not currently indicated.

*Twice daily regimen resulted in greatest reduction in fasting plasma glucose and HbA1c.

Special Dosing Considerations

Renal Impairment:

- No dose adjustment in patients with renal dysfunction is recommended with pioglitazone or rosiglitazone.

Hepatic Impairment:

- Both pioglitazone and rosiglitazone therapy should not be initiated if a patient exhibits clinical evidence of active liver disease or serum transaminase levels (ALT) exceed 2.5 times the upper limit of normal.

Other:

- The safety and efficacy of pioglitazone and rosiglitazone in pediatric patients has not been established.
- Pioglitazone and rosiglitazone are both pregnancy category C drugs.
- Manufacturers recommendations for pioglitazone and rosiglitazone do not designate whether the tablets can be crushed. GlaxoSmithKline has not studied the efficacy or bioequivalence of crushed or broken rosiglitazone tablets.

VI. Comparative Effectiveness

There are no head-to-head trials comparing the clinical efficacy of pioglitazone to that of rosiglitazone.

Table 8. Additional Outcomes Evidence for the Thiazolidinediones

Study	Sample	Duration	Results
Rosiglitazone and glyburide on cardio function and glycemic control[78]	n=203	52 week open-label, active-controlled study	In looking at the cardiovascular and antihyperglycemic effects of rosiglitazone 4mg BID versus glyburide (mean 10.5mg QD): • Neither treatment produced an increase in left ventricular mass index that exceeded 1 SD and ejection fraction did not change in either group. • Both groups had clinically insignificant increases in left ventricular end-diastolic volume. • Avandia, but not glyburide, caused a statistically significant reduction in ambulatory diastolic blood pressure.
Rosiglitazone plus glibenclamide (glyburide) vs. upward titration of glibenclamide[79]	n=340	26 week randomized trial	After 26 weeks of treatment with rosiglitazone (8mg QD) plus glyburide (7.5mg QD) or glyburide (max 15mg QD): • The rosiglitazone/glyburide combination reduced HbA1c by 0.81% (P<0.0001) and fasting plasma glucose by 2.4mmol/L (P<0.0001) compared with glyburide monotherapy. • With rosiglitazone combination and glibenclamide monotherapy, the total cholesterol: HDL ratio was reduced by 5 and 13% and triglycerides were reduced by 6 and 2%, respectively.

Pioglitazone and rosiglitazone monotherapy and combination therapy[80]	-	Multicenter, retrospective chart review of 1,115 records	This retrospective chart review, was performed to evaluate and compare the effects of pioglitazone and rosiglitazone monotherapy and combination therapy on blood lipid levels and HbA1c in patients with type 2 diabetes: • Of the patients who received pioglitazone, 83% also received >/=1 other antihyperglycemic agent and 59% received some form of antihyperlipidemic therapy. • Among those who received rosiglitazone, 81% received concomitant antihyperglycemic medication and 60% received some form of antihyperlipidemic therapy. • With pioglitazone, mean levels of serum triglyceride, total cholesterol, and LDL-C decreased and HDL-C increased in most patients, with or without concomitant antihyperglycemic medications; with rosiglitazone, with or without other antidiabetic agents, triglyceride and HDL-C levels decreased, whereas total cholesterol and LDL-C levels increased in most patients. • Reductions in HbA1c and increases in body weight related to each study drug were comparable.
Thiazolidine-diones and blood lipids[81]	n=5,304	Summary analysis of published, double-blind, placebo-controlled studies	When data from 19 studies of pioglitazone and rosiglitazone were analyzed by the random-effects model: • Subjects treated with pioglitazone were more obese and showed more pronounced hyperglycemia and dyslipidemia (increased triglycerides and decreased HDL cholesterol) at baseline than did subjects treated with rosiglitazone. • Studies with pioglitazone showed greater beneficial effects on triglycerides, total cholesterol, and LDL cholesterol, after adjustment for the respective lipid levels at baseline. • Rosiglitazone 8 mg QD showed greater increases in total cholesterol and LDL cholesterol than did rosiglitazone 4 mg QD. Pioglitazone 30 mg QD showed greater reductions in triglycerides than did pioglitazone 15 mg QD. • Studies conducted with pioglitazone showed more beneficial effects on blood lipids, but also different study population characteristics in comparison with studies conducted with rosiglitazone. Differences in the study population between the groups may have contributed to the results seen.
Addition of pioglitazone vs. NPH insulin to max. doses of sulfonylurea and metformin[82]	n=62	16 week open label, randomized controlled trial	In comparing the efficacy of pioglitazone versus NPH insulin in addition to sulfonylurea and metformin: • HbA1c levels were lowered to a similar degree in each treatment arm (pioglitazone: -1.9% +/- 1.5%; insulin: -2.3% +/- 1.5%; P = 0.32), but hypoglycemia was less common among patients who received pioglitazone than those who received insulin (37% [11/30] vs. 68% [19/28], P=0.02). • Pioglitazone, but not insulin, resulted in an increase in high-density lipoprotein (HDL) cholesterol levels. • Both treatments had similar effects on weight, other lipid values, blood pressure, and urine microalbumin levels.
Effects of pioglitazone, metformin, and gliclazide (glipizide) on lipoprotein subfractions[83]	n=60	9 month randomized trial	Type 2 diabetics not on lipid-lowering drugs were randomized to pioglitazone, metformin or glipizide and monitored for changes in cholesterol profile: • HbA1c, triglycerides, glucose, and cholesterol levels were comparable across groups at baseline and over time. • LDL(3) mass and the LDL(3)-to-LDL ratio fell with pioglitazone (LDL(3) mass 36.2 to 28.0 mg/dl, P < 0.01; LDL(3)-to-LDL 19.2:13.3%, P < 0.01) and metformin (42.7 to 31.5 mg/dl, P < 0.01; 21.3:16.2%, P < 0.01, respectively) with no change on glipizide. • Total HDL cholesterol increased on pioglitazone (1.28 to 1.36 mmol/l, P = 0.02) but not glipizide (1.39 to 1.37 mmol/l, P = NS) or metformin (1.26 to 1.18 mmol/l, P = NS), largely due to an HDL(2) increase (0.3 to 0.4 mmol/l, P < 0.05). • HDL(3) cholesterol fell on metformin (0.9 to 0.85 mmol/l, P < 0.01). • On pioglitazone and metformin, the HDL(2)-to-HDL(3) ratio increased compared with no change on glipizide.

Thiazolidine-dione therapy in the prevention of type 2 diabetes[84]	n=172	3 year prospective study	In evaluating the early effect of thiazolidinedione (TZD) treatment in the prevention or delay of type 2 diabetes in patients with impaired glucose tolerance and insulin resistance: • Mean HbA1c and C-peptide levels decreased for patients receiving either TZD at the 2-year assessment, and reductions were maintained at study end point. • After 2 years, none of the patients receiving a TZD progressed to type 2 diabetes. By the end of the 3rd year, 3 patients progressed to type 2 diabetes by study end. • In the study control group, 11 patients became diabetic after 2 years and 19 patients became diabetic by the study end. • The incidence of diabetes after 3 years was 88.9% lower in the TZD group compared with the control group ($p<0.001$).

Additional Evidence

Dose Simplification: Not Applicable.

Stable Therapy: No peer reviewed studies (as listed in Medline/Pubmed or Ovid) are available regarding changing from pioglitazone to rosiglitazone or from rosiglitazone to pioglitazone. Additionally, no studies have evaluated the efficacy of changing from a thiazolidinedione to another oral antidiabetic agent.

When either rosiglitazone or pioglitazone is added to existing therapy, the current dose of sulfonylurea, metformin, or insulin, can be continued upon initiation of the thiazolidinedione.

Impact on Physician Visits: No peer reviewed studies (as listed in Medline/Pubmed or Ovid) have evaluated the thiazolidinediones and their impact on medical resources such as physician visits.

VII. Conclusions

The FDA approved indications are similar for pioglitazone and rosiglitazone as are their dosing schedules, although rosiglitazone has demonstrated better efficacy given twice daily as compared to once daily dosing. In clinical trials, the incidence of edema in rosiglitazone plus insulin (14.7%) versus pioglitazone plus insulin (15.3%) was similar, however, this data is not from head-to head trials. The thiazolidinediones as a class have retained liver toxicity precautions due to the postmarketing reports of hepatic toxicity with Rezulin. In looking at drug interactions, rosiglitazone does not inhibit any of the major P450 enzymes, where pioglitazone is thought to be a weak inducer of the CYP450 3A4 substrate.

As there are no direct comparative studies available to compare the true efficacy and effect of pioglitazone and rosiglitazone on cholesterol levels, head-to-head studies are needed to place advantages on one drug over the other. However, previously mentioned studies showed the thiazolidinedione class in general may be beneficial on diastolic blood pressure, the cholesterol profile, and on the incidence of hypoglycemia, as compared to other antidiabetic agents. Recent evidence from a July 2004 study suggests that progression of insulin resistance and impaired glucose tolerance to type 2 diabetes appears to be significantly delayed or prevented with early thiazolidinedione therapy.[84] Therefore, the drugs within the thiazolidinedione class offer significant clinical advantage in general use but are comparable to each other.

VIII. Recommendations

Medicaid should work with manufacturers of pioglitazone (Actos®) and rosiglitazone (Avandia®) on cost proposals so that at least one brand of pioglitazone or rosiglitazone is selected as a preferred agent.

Antidiabetic Combination Agents

I. Comparative Indications of the Antidiabetic Combination Agents

There are three antidiabetic combination products, all containing metformin plus another oral antidiabetic agent. A generic form of Glucovance has become available since the May P&T meeting. This review encompasses all dosage forms and strengths. Table 1 lists the agents in this review.

Table 1. Antidiabetic Combination Products in this Review

Generic Name*	Formulation	Example Brand Name
Metformin / rosiglitazone	Oral	Avandamet
Metformin / glyburide	Oral	Glucovance*
Metformin / glipizide	Oral	Metaglip

*Generic Available.

The safety and efficacy of metformin/rosiglitazone as initial pharmacologic therapy for patients with type 2 diabetes after a trial of caloric restriction, weight loss, and exercise has not been established.

Table 2. FDA-Approved Indications for the Antidiabetic Combination Agents[3, 47]

	Adjunct to Diet and Exercise in Type 2 Diabetes	Initial Therapy, as an Adjunct to Diet and Exercise, When Response is Poor with Diet and Exercise Alone	Second-Line Therapy When Diet and Exercise, and Monotherapy with a Sulfonylurea or Metformin, do not Provide Adequate Glycemic Control	Combination Therapy with Thiazolidinediones
Metformin / rosiglitazone (Avandamet)	✓*			
Metformin / glyburide (Glucovance)		✓	✓	✓
Metformin / glipizide (Metaglip)		✓	✓	

* In patients already treated with combination metformin and rosiglitazone or who are not adequately controlled on metformin alone.

Combination products containing metformin retain the same warnings as documented with metformin monotherapy. The combination products should be temporarily discontinued in patients undergoing radiologic studies involving iodinated contrast materials. Metformin should not be initiated in patients >80 years of age unless renal function is not reduced. The lactic acidosis black box warning with metformin also applies to the combination products. Specific details are available on page 12 of the biguanide single-entity review. Warnings pertaining to edema and congestive heart failure with the thiazolidinediones also apply to Avandamet.

Table 3. Contraindications of the Antidiabetic Combination Agents

	Known Sensitivity to the Drug	Renal Disease/Dysfunction	Congestive Heart Failure	Acute or Chronic Metabolic Acidosis
Metformin / rosiglitazone (Avandamet)	✓	✓	✓	✓
Metformin / glyburide (Glucovance)	✓	✓	✓	✓
Metformin / glipizide (Metaglip)	✓	✓	✓	✓

II. Pharmacokinetic Parameters

Metformin / Rosiglitazone (Avandamet)
In a bioequivalence and dose proportionality study of Avandamet 4mg/500mg, both the rosiglitazone component and the metformin component were bioequivalent to coadministered 4mg rosiglitazone maleate tablet and the 500mg metformin hydrochloride tablet under fasting conditions.[47] The pharmacokinetics of both the rosiglitazone component and the metformin component of Avandamet when taken with food were similar to the pharmacokinetics of both drug when administered concomitantly as separate tablets with food. Table 4 further compares the single entity drugs with the combination product with regard to important pharmacokinetic parameters. Information on the distribution, metabolism and excretion of the components of Avandamet is similar to that of the single-entity drug components.

Table 4. Pharmacokinetic Parameters for Rosiglitazone and Metformin[47]

Regimen	N	AUC (0-inf) (ng.h/ml)	C_{max} (ng/ml)	T_{max} (h)*	T1/2 (h)
Rosiglitazone					
A	25	1442 (324)	242 (70)	0.95 (0.48-2.47)	4.26 (1.18)
B	25	1398 (340)	254 (69)	0.57 (0.43-2.58)	3.95 (0.81)
C	24	349 (91)	63 (15)	0.57 (0.47-1.45)	3.87 (0.88)
Metformin					
A	25	7116 (2096)	1106 (329)	2.97 (1.02-4.04)	3.46 (0.96)
B	25	7413 (1838)	1135 (253)	2.50 (1.03-3.98)	3.36 (0.54)
C	24	6945 (2045)	1080 (327)	2.97 (1.00-5.98)	3.35 (0.59)

*Median and range presented for T_{max}
Regimen Key: A = 4mg/500mg Avandamet
B = 4mg rosiglitazone tablet + 500mg metformin tablet
C = 1mg/500mg Avandamet

Metformin / Glyburide (Glucovance)
In bioavailability studies of Glucovance 2.5mg/500mg and 5mg/500mg, the mean area under the plasma concentration time curve (AUC) for the glyburide component was 18% and 7%, respectively, greater than that of the Micronase® brand of glyburide coadministered with metformin.[47] Therefore**,** the glyburide component of Glucovance is not bioequivalent to Micronase®, however, the metformin component of Glucovance is bioequivalent to metformin coadministered with glyburide. Glucovance bioequivalence has not been established with single ingredient glyburide products. Distribution, metabolism and elimination of Glucovance is reported similarly with that of each single entity drug. In a randomized, double-blind, two-way crossover study looking at the differences in pharmacokinetics and pharmacodynamics of Glucovance and glyburide plus metformin, treatment with Glucovance resulted in significantly smaller mean postprandial glucose excursion than was attained by treatment with glyburide plus metformin (P=0.011).[85] The mean glyburide concentration was significantly greater (approximately 16%) after Glucovance than glyburide/metformin on both days 1 and 14. This study also showed Glucovance was associated with a 2-fold greater area under the curve to 3 hours for glyburide (P<0.001), however, the AUC administration interval was equivalent for both formulations.

Metformin / Glipizide (Metaglip)
In a single dose study in healthy subjects, the glipizide and metformin components of Metaglip 5mg/500mg were bioequivalent to coadministered Glucotrol® and Glucophage®.[39]

III. Drug Interactions of the Combination Antidiabetic Products

Drug interactions with the combination antidiabetic products can be extrapolated from those interactions identified and documented for the single entity agents. The single entity agents have been covered in this review, however, a summary of each single entity medication or class has been included below. Clinically significant (level 1 and level 2) drug interactions can be referenced in the respective single entity review.

Avandia (rosiglitazone)
In vitro drug metabolism studies indicate that rosiglitazone does not inhibit any of the major P450 enzymes at clinically relevant concentrations. Rosiglitazone was also shown to have no clinically relevant effect when given with the following drugs: nifedipine, oral contraceptives, glyburide, metformin, acarbose, digoxin, warfarin, ethanol, and ranitidine.[47]

Glucophage (metformin)
Multiple studies have documented interactions with the biguanide medications. Cationic drugs (amiloride, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim and vancomycin) that are eliminated by renal tubular secretion, theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems.[23, 47] This type of interaction has been documented specifically with cimetidine, where there was a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin area under the curve (AUC). Careful monitoring and dosage adjustments with metformin may be necessary.

Metformin also interacts with certain drugs known to product hyperglycemia, leading to loss of glycemic control. These drugs include thiazide and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. Close monitoring is necessary when these drugs are added or removed from treatment protocols of diabetic patients. Less significant documented interactions with metformin include: acarbose, atropine, belladonna, benztropine, biperiden, dicyclomine, hyoscyamine, oxybutynin, procyclidine and propantheline.

Sulfonylureas (glipizide and glyburide)
The hypoglycemic affect of sulfonylureas may be enhanced due to decreased hepatic metabolism, inhibition of renal excretion, displacement from protein-binding sites (NSAIDs and azoles), decreased blood glucose, and alteration of carbohydrate metabolism. In contrast, the hypoglycemic effects may be decreased when there is a increase in hepatic metabolism, a decrease in insulin release, and an increased renal excretion. Documented, but less severe interactions have occurred with the following drugs or classes of drugs: Clofibrate, Fenfluramine, Urinary acidifiers, androgens, cholestyramine, cyclosporine, digoxin, fluvoxamine, gemfibrozil, H-2 blockers, macrolide antibiotics, omeprazole, probenecid, quinolones (ciprofloxacin), and tricyclic antidepressants.

IV. Adverse Drug Events with the Combination Antidiabetic Agents

The combination antidiabetic agents have been compared to their respective monotherapies with regard to adverse effects. The following tables demonstrate adverse effect profiles for each combination agent compared to that of the equivalent monotherapies. Generally, the combination antidiabetic agents tend to result in a higher incidence of hypoglycemia as compared to monotherapy.

In double-blind studies, hypoglycemia was reported more frequently in patients receiving metformin and rosiglitazone combination, compared to metformin or rosiglitazone monotherapies. Table 5 compares other common adverse effects for the monotherapies versus the combination. (Note: In this study, Avandamet was not used, only the combination of metformin plus rosiglitazone). In addition, edema was reported in 4.8% of patients receiving rosiglitazone, 1.3% on placebo, 2.2% on metformin monotherapy, and 4.4% with rosiglitazone in combination with maximum doses of metformin.

Table 5. Comparison of Adverse Events (%) for Rosiglitazone, Metformin and the Combination[47]

Adverse Event	Rosiglitazone Monotherapy n=2,526	Placebo n=601	Metformin monotherapy n=225	Rosiglitazone Plus Metformin n=338
Body as a Whole				
Headache	5.9	5.0	8.9	6.5
Back Pain	4.0	3.8	4.0	5.0
Arthralgia	3.0	4.0	2.2	5.0
Digestive System				
Diarrhea	2.3	3.3	15.6	12.7
Respiratory System				
URI	9.9	8.7	8.9	16.0
Sinusitis	3.2	4.5	5.3	6.2
Viral infection	3.2	4.0	3.6	5.0
Endocrine				
Hypoglycemia	0.6	0.2	1.3	3.0
Hyperglycemia	3.9	5.7	4.4	2.1
Other: Injury	7.6	4.3	7.6	8.0
Fatigue	3.6	5.0	4.0	5.9
Anemia	1.9	0.7	2.2	7.1

Table 6. Comparison of Treatment Emergent Symptoms in a Placebo and Active Controlled Trial of Glucovance as Initial Therapy[47]

Variable	Placebo n=161	Glyburide n=160	Metformin n=159	Glucovance 1.25mg/250mg n=158	Glucovance 2.5mg/500mg n=162
Mean Final Dose	0mg	5.3mg	1317mg	2.78mg/557mg	4.1mg/824mg
Number (%) of patients with symptoms of hypoglycemia	5 (3.1)	34 (21.3)	5 (3.1)	18 (11.4)	61 (37.7)
Number (%) of patients with gastrointestinal adverse events	39 (24.2)	38 (23.8)	69 (43.3)	50 (31.6)	62 (38.3)

Table 7. Adverse Events >5% for Metaglip, Metformin and Glipizide[47]

Adverse Event Number (%) of Patients	Glipizide 5mg Tablets n=170	Metformin 500mg Tablets n=177	Metaglip 2.5mg/250mg Tablets n=172	Metaglip 2.5mg/500mg Tablets n=173
URI	12 (7.1)	15 (8.5)	17 (9.9)	14 (8.1)
Diarrhea	8 (4.7)	15 (8.5)	4 (2.3)	9 (5.2)
Dizziness	9 (5.3)	2 (1.1)	3 (1.7)	9 (5.2)
Hypertension	17 (10.0)	10 (5.6)	5 (2.9)	6 (3.5)
Nausea / Vomiting	6 (3.5)	9 (5.1)	1 (0.6)	3 (1.7)

In a controlled trial of Metaglip 2.5mg/250mg and 2.5mg/500mg, the number of patients with hypoglycemia were 2.9% for glipizide, 0% for metformin, 7.6% for Metaglip 2.5mg/250mg, and 9.3% for Metaglip 2.5mg/500mg, with 2.6% of patients discontinuing Metaglip due to hypoglycemic symptoms.[47]

V. Dosing and Administration for the Combination Antidiabetic Agents

Dosing with combination agents should be individualized and should correspond to the same dosing (especially with Avandamet) as given with the single entity components. Dosing should be initiated low and gradually titrated, so the minimal effective dose can be determined. The dosing schedules for the combination agents are similar.

Table 8. Dosing for the Combination Antidiabetic Agents[3, 24, 47]

	Availability	Dose /Frequency/Duration
Metformin / rosiglitazone (Avandamet)	1mg/500mg, 2mg/500mg, and 4mg/500mg Tablets	Starting: Initial dosing should be based on the patient's current dose of Avandia and metformin monotherapy doses, while not exceeding the maximum daily dose.* Avandamet should be given in divided doses with meals. Titration: metformin dose is Q 1-2 weeks Avandia dose is Q 8-12 weeks Maximum: 8mg Avandia/2000mg metformin daily
Metformin / glyburide (Glucovance)	1.25mg/250mg, 2.5mg/500mg, and 5mg/500mg Tablets	Starting Initial Therapy: 1.25mg/250mg QD-BID with meals Starting Second-Line Therapy: 2.5mg/500mg or 5mg/500mg BID Titration: 1.25mg/250-5mg/500mg QD every 2 weeks Maximum: 20mg glyburide / 2000mg metformin daily
Metformin / glipizide (Metaglip)	2.5mg/250mg, 2.5mg/500mg, and 5mg/500mg Tablets	Starting Initial Therapy : 2.5mg/250mg QD with meals If FPG is 280-320mg/dl start at 2.5mg/500mg BID Starting Second-Line Therapy: 2.5mg/500mg BID or 5mg/500mg BID Titration: Increments of one tablet per day every 2 weeks, in divided doses Maximum: 20mg glipizide / 2000mg metformin daily

*Avandamet is not indicated in as initial therapy in patients who have not been stabilized with Avandia and metformin.

Special Dosing Considerations

Renal and Hepatic Impairment:

- Metformin products should not be used in patients with renal disease or dysfunction or in those with hepatic disease.
- No dose adjustment in patients with renal dysfunction is recommended with rosiglitazone.
- Rosiglitazone therapy should not be initiated if a patient exhibits clinical evidence of active liver disease or serum transaminase levels (ALT) exceed 2.5 times the upper limit of normal.
- In general, initial doses of sulfonylureas in patients with renal or hepatic disease should be more conservative to avoid hypoglycemic reactions.

Other:

- Metformin is a pregnancy category B while the other agents are pregnancy category C drugs.
- GlaxoSmithKline reports no studies have been performed to document the efficacy or bioequivalence of administration of broken or crushed metformin / rosiglitazone (Avandamet) tablets.

VI. Comparative Effectiveness of the Combination Antidiabetic Agents

Comparison trials evaluating the efficacy of the combination antidiabetic tablet formulation versus treatment with co-administration of each individual drug have not frequently been performed. There is very limited data available to make this efficacy comparison. Much of the data available and presented in product package inserts compares monotherapy to combination treatment.

Metformin / Rosiglitazone (Avandamet)

There have been no clinical efficacy trials conducted with Avandamet tablets. Studies using the separate components have established the effective and safe use, and the additive benefit of rosiglitazone when added to a regiment of maximum doses of metformin. Table 9 illustrates the glycemic parameters of metformin monotherapy compared to rosiglitazone plus metformin. The difference in fasting plasma glucose (FPG) and HbA1c was statistically significant ($P<0.0001$) for combination therapy when compared to metformin alone.

Table 9. Glycemic Parameters in a 26-week Rosiglitazone + Metformin Combination Study[47]

	Metformin	Rosiglitazone 4mg QD + Metformin	Rosiglitazone 8mg QD + Metformin
n=	113	116	110
FPG (mg/dl)			
Baseline (mean)	214	215	220
Change from baseline (mean)	6	-33	-48
HbA1c (%)			
Baseline (mean)	8.6	8.9	8.9
Change from baseline (mean)	0.5	-.06	-0.8

Metformin / Glyburide (Glucovance)

The results of a 20-week, double-blind, multicenter clinical trial of 806 drug-naïve patients who were given placebo, 2.5mg glyburide, 500mg metformin, Glucovance 1.25mg/250mg or Glucovance 2.5mg/500mg provided the results seen in Table 10.[47] Treatment with Glucovance resulted in significantly greater reduction in HbA1c and postprandial plasma glucose compared to glyburide, metformin or placebo. Glucovance also resulted in greater reduction in fasting plasma glucose compared to glyburide, metformin or placebo, but the differences from glyburide and metformin did not reach statistical significance.

Table 10. Placebo and Active-Controlled Trial of Glucovance as Initial Therapy[47]

	Placebo n=147	Glyburide 2.5mg n=142	Metformin 500mg n=141	Glucovance 1.25mg/250mg n=149	Glucovance 2.5mg/500mg n=152
Mean Final Dose	0mg	5.3mg	1317mg	2.78mg/557mg	4.1mg/834mg
HbA1c					
Baseline Mean %	8.14	8.14	8.23	8.22	8.20
Mean Change from Baseline	-0.21	-1.24	-1.03	-1.48	-1.53
Fasting Plasma Glucose					
Baseline Mean FPG (mg/dl)	177.2	178.9	175.1	178	176.6
Mean Change from Baseline	4.6	-35.7	-21.2	-41.5	-40.1
Body Weight Mean Change	-0.7kg	+1.7kg	-0.6kg	+1.4kg	+1.9kg
Final HbA1c Distribution (%)	19.7	59.9	50.4	66.4	71.1
≤7%	37.4	26.1	29.8	25.5	19.1
>7 and <8%	42.9	14.1	19.9	8.1	9.2
≥8%					

Metformin / Glipizide (Metaglip)

In a 24-week, double blind, active-controlled, multicenter trial, patients were given glipizide 5mg, metformin 500mg, Metaglip 2.5mg/250mg, or Metaglip 2.5mg/500mg. Table 11 illustrates the results of the different treatments on glycemic control. Treatment with Metaglip resulted in significantly greater reduction in HbA1c compared to glipizide and to metformin therapy. Metaglip also resulted in significantly greater reductions in fasting plasma glucose versus metformin therapy.

Table 11. Active-Controlled Trial of Metaglip as Initial Therapy[47]

	Glipizide 5mg n=168	Metformin 500mg n=171	Metaglip 2.5mg/250mg n=166	Metaglip 2.5mg/500mg n=163
Mean Final Dose	16.7mg	1749mg	7.9mg/791mg	7.4mg/1477mg
HbA1c: Baseline Mean %	9.17	9.15	9.06	9.10
Mean Change from Baseline	-1.77	-1.46	-2.15	-2.14
Fasting Plasma Glucose				
Baseline Mean FPG (mg/dl)	210.7	207.4	206.8	203.1
Mean Change from Baseline	-46.2	-42.9	-54.2	-56.5

The additional relevant clinical evidence in the literature has been presented in Table 7.

Table 12. Additional Outcomes Evidence for the Combination Antidiabetic Agents

Study	Sample	Duration	Results
Addition of rosiglitazone to Metformin[86]	n=550	Data pooled analysis from two double-blind studies	In evaluating the efficacy of rosiglitazone when added to near maximum doses of metformin, in obese insulin-resistant patients: • Rosiglitazone improved HbA1c and fasting plasma glucose to a clinically significant extent; the effect was most pronounced in the obese patients. • Improvements in estimates of insulin resistance and beta-cell function were greatest in obese patients, as were reductions in fasting insulin.
Glyburide/ metformin tablets vs. glyburide Co-administered with metformin in type 2 diabetes[87]	n=950	Retrospective cohort study using pharmacy claims and corresponding lab results from Aug 2000-July 2001	In comparing the change in HbA1c with combination therapy fixed-dose glyburide/metformin tablets versus glyburide co-administered with metformin: • The mean decrease from baseline HbA1c, adjusted for baseline HbA1c and dosage, of 2.02% for glyburide/metformin tablets was significantly ($P < 0.0001$) greater than the decrease of 1.49% for glyburide co-administered with metformin. • Glyburide/metformin patients with baseline HbA1c >/= 8% experienced a significantly ($P < 0.0001$) greater decrease in HbA1c of 2.93% compared to 1.92% for glyburide co-administered with metformin. • For patients with baseline HbA1c < 8%, the difference between the HbA1c responses remained significant, even though reductions in HbA1c were smaller for both glyburide/metformin tablets and glyburide co-administered with metformin (0.54% and 0.23%, $P = 0.0017$). • Patients were more adherent with glyburide/metformin tablets ($P < 0.0001$). **Adherence was not a significant predictor of change in HbA1c.**
Sulfonylurea plus metformin vs. fixed-dose glyburide-metformin tablet[88]	n=72	Retrospective cohort study	In evaluating the change in HbA1c in patients with type 2 diabetes switched from coadministration of a sulfonylurea (glyburide or glipizide) and metformin, to a single glyburide-metformin tablet: • The mean reduction in HbA1c was 0.6% (P=0.002) at a mean follow-up of 196 days after the switch to glyburide-metformin tablets. • Improvement in glycemic control was predominantly seen in patients with a baseline HbA1c ≥ 8% in whom a 1.3% mean reduction in HbA1c (P=0.0002) was achieved despite a lower mean final dose of glyburide. • Summary: This study suggests that use of glyburide-metformin tablets versus coadministration of a sulfonylurea plus metformin may provide an improvement in glycemic control in a range of 1.2 to 1.4 absolute percentage point decrease in HbA1c.
Benefits on glycemia of adding rosiglitazone rather than glyburide to metformin[89]	n=141	24 week randomized, double-blind study	The effects of two glucose-lowering agents (rosiglitazone and glyburide) were evaluated on cognitive function, efficacy and safety, when added to metformin therapy: • After 24 weeks, similar reductions in fasting plasma glucose were observed (38.2 +/- 5.4mg/dL (MET+RSG); 41.6 +/- 5.2mg/dL (MET+GLY)). • Insulin sensitivity increased by a median of 9.4% with MET+RSG compared to a median decline of 0.1% with MET+GLY. • Episodes of hypoglycemia were approximately 4.5 fold more common with MET+GLY (13.3%), compared to MET+RSG (2.9%). • GI events were more frequent with MET+GLY (25.3%) than with MET+RSG (14.3%). • No difference in weight gain was observed between the groups after 24 weeks of treatment.

. **Additional Evidence**

Dose Simplification:

Avandamet: Limited data is available in the literature addressing adherence with the fixed-dose product versus each separate drug.[90] One study analyzed the effect of the rosiglitazone/metformin fixed dose tablet on medication adherence and showed that in 3,158 patients, subjects switched from monotherapy (with either metformin or rosiglitazone) to the fixed dose combination tablet exhibited a statistically significant higher post-index medication possession ratio (86%) than subjects switching from monotherapy to combination therapy (rosiglitazone plus metformin in separate dosage forms) (61%, $p<0.0001$). No studies have evaluated the effect of adherence on HbA1c for Avandamet.

Glucovance: One study has evaluated the comparative efficacy of the fixed dose combination tablet with each respective monotherapy agent. The study listed above (reference #87) in table 12 is the only published study evaluating the fixed-dose glyburide/metformin tablet to combination treatment with each individual agent. The study reported patients were more adherent with the fixed-dose product ($P<0.0001$) and saw statistically significant ($P<0.0001$) reductions in HbA1c.
Metaglip: The study listed in table 12 (reference #88) did not measure adherence differences between the fixed-dose product and coadministration of a sulfonylurea plus metformin. Prospective studies are needed to measure the adherence rates and to determine the precise effect of the fixed-dose product.

Stable Therapy: No studies have been performed specifically examining the safety and efficacy of rosiglitazone/metformin (Avandamet) in patients previously treated with other oral hypoglycemic agents and switched to Avandamet.[47] The manufacturers prescribing instructions for each combination agent states the daily doses of each individual drug should not be exceeded when switching to a fixed-dose combination tablet.
Researchers from several studies comparing the efficacy and safety of glyburide / metformin (Glucovance) with that of either glyburide or metformin alone had recommended the following algorithm for switching patients who are already receiving treatment with metformin and / or a sulfonylurea to Glucovance:[91]

- In patients who have failed to attain good glycemic control despite monotherapy with at least half-maximal dosages of metformin or a sulfonylurea, treatment should begin with Glucovance 2.5mg/500mg given twice daily, and the dose should be titrated as necessary at 1-2 week intervals based on patients' self-monitored blood glucose values.
- Patients who are already receiving a sulfonylurea and metformin as separate medications and have failed to achieve targeted glycemic control should be switched to Glucovance 2.5mg/500mg or 5mg/500mg at a dose that is closest (mg for mg) to the metformin dose and an equivalent sulfonylurea dose, but not to exceed the total daily doses already taken. The dose should then be titrated as necessary.
- Patients who are already well controlled by combination treatment with a sulfonylurea and metformin as separate medications, but may prefer to take or benefit from taking a fixed combination tablet, should be switched to Glucovance at a dose that is closest (mg to mg) to the sulfonylurea dose and the metformin dose. The dose should then be titrated as necessary.

Impact on Physician Visits: No peer reviewed studies were found in a literature search of Medline/Pubmed and Ovid specifically evaluating use of the agents in this class and physician visits or medical service utilization.

VII. Conclusions

The combination antidiabetic tablet formulations, except for the glyburide component of metformin/glipizide (Glucovance), have been proven bioequivalent to their individual drug components. The glyburide component of Glucovance is not bioequivalent to Micronase. The indications for metformin/glyburide and metformin/glipizide are similar, with that of metformin/rosiglitazone being the most limiting, with use only in patients stabilized on metformin and rosiglitazone prior to use of the single tablet formulation. There are no clinically significant drug interactions or adverse events that make one product more advantageous over another. Finally, more clinical efficacy studies comparing the fixed-dose products with their respective monotherapies are becoming available. Studies support use of the fixed-dose glyburide/metformin (Glucovance) product over glyburide co-administered with metformin, due to benefits on HbA1c. Additionally, a generic formulation is newly available for the fixed-dose glyburide/metformin (Glucovance) product. As a result, all brand products within the class reviewed are comparable to each other and offer no significant advantage over other alternatives in general use.

VIII. Recommendations

No brand combination antidiabetes agent is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Alzheimer's Agents
Cholinesterase Inhibitors, NMDA Receptor Antagonists
AHFS 120400, AHFS 289200
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I. Overview

Alzheimer's disease (AD) is a progressive dementia affecting both cognition and behavior. A person with AD eventually loses his or her very identity, not just memories, but all associated cognitive, analytical, and physical functioning. AD is classified under Delirium, Dementia, and Amnestic and Other Disorders in the *Diagnostic and Statistical Manual for Mental Disorders*, 4th edition (DSM-IV-TR). The exact pathophysiologic mechanisms behind the disease are not entirely understood, and the available drugs reduce symptoms for a period of time, with the disease eventually ending fatally. AD (through indirect complications such as sepsis, pneumonia, choking, nutritional deficiencies, and trauma) is the fourth leading cause of death in U.S. elderly patients.[1]

AD patients become totally dependent on a family member, spouse, or other caregiver for all basic needs. More than 4 million people in the United States have AD and it is the most common cause of dementia.[1] Most cases of AD occur in individuals older than 65, however, in about 5% of cases onset can be as early as age 40, resulting in early onset (ages 40-64 years) disease. The disease affects two times as many women as men, although genetic inheritance is the primary mode of transmission, along with several environmental factors (stroke, alcohol abuse, small head circumference, repeated or severe head trauma, and lower levels of education). The average survival period after diagnosis is 3.3 years.

By 2050, one in five people will be over age 65 years, and the number of Alzheimer's patients is projected to be 14 million.[1] Because there is no definitive diagnosis laboratory, clinical, or imaging tests available, AD remains a diagnosis of exclusion. Treatment consists of nonpharmacologic and pharmacologic therapies, with nonmedical interventions as the current primary interventions for management of AD due to the profound effect of the illness on the patient and family. Medications are used in the context of multimodal interventions, and in 2002, accounted for 8.2 prescriptions per 1000 members.[2] Available pharmacotherapeutic treatments are for the most part symptomatic attempts to either improve or maintain cognition, although there is some evidence that vitamin E and cholinesterase inhibitors may prolong the time to critical functional endpoints. Secondary pharmacotherapeutic interventions are used to treat depression, psychosis, and agitation. No medications are available to change the course of illness.

There are four cholinesterase inhibitor medications that will be reviewed for the treatment of AD. Namenda, a NMDA receptor antagonist, is newly eligible for review since the May P&T meeting. Due to similar FDA approved indications, the cholinesterase inhibitors and NMDA receptor antagonists are being reviewed together. At this time, there are no generic alternatives to any of the Alzheimer's medications. This review encompasses all dosage forms and strengths.

Table 1. Alzheimer's Agents in this Review

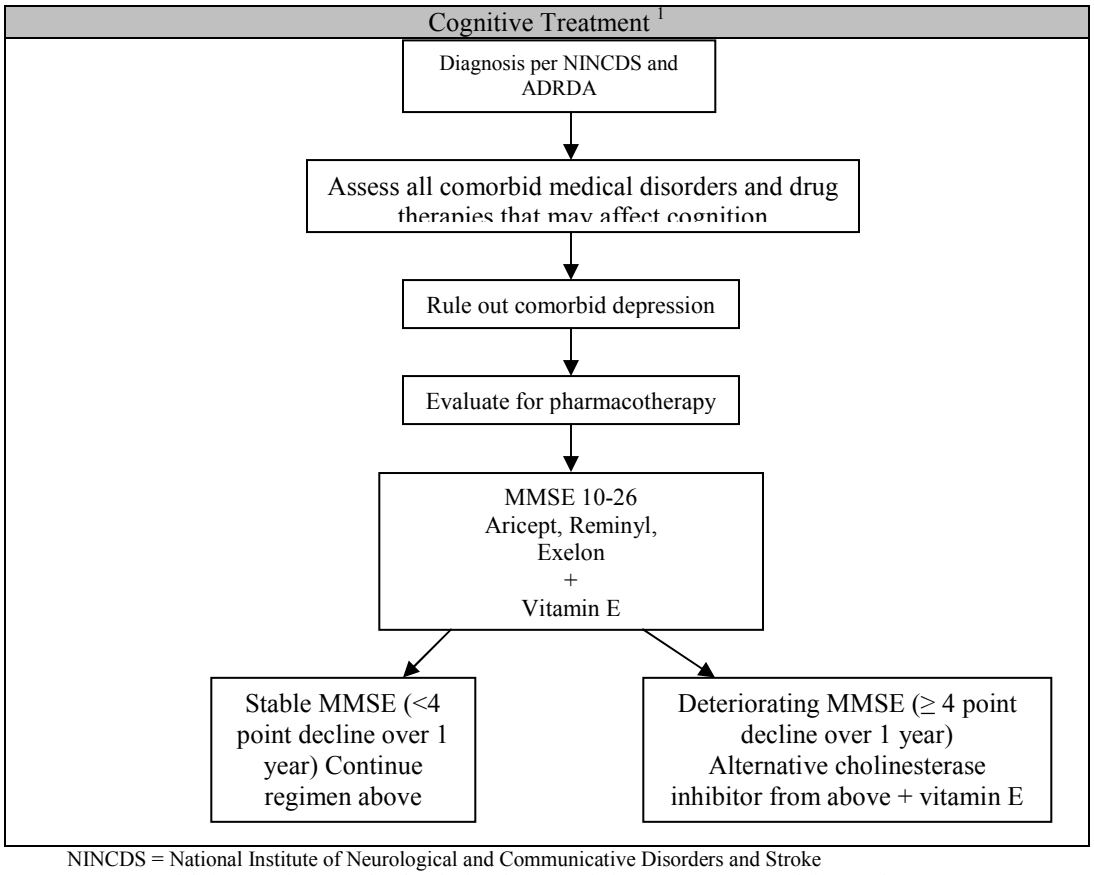
Drug Classification	Generic Name*	Formulation	Example Brand Names
Cholinesterase Inhibitor	Donepezil HCl	Oral	Aricept
	Tacrine HCl	Oral	Cognex
	Rivastigmine Tartrate	Oral	Exelon
	Galantamine Hydrobromide	Oral	Reminyl
NMDA Receptor Antagonist	Memantine	Oral	Namenda

*There are no generic formulations available for any of the medications in this class.

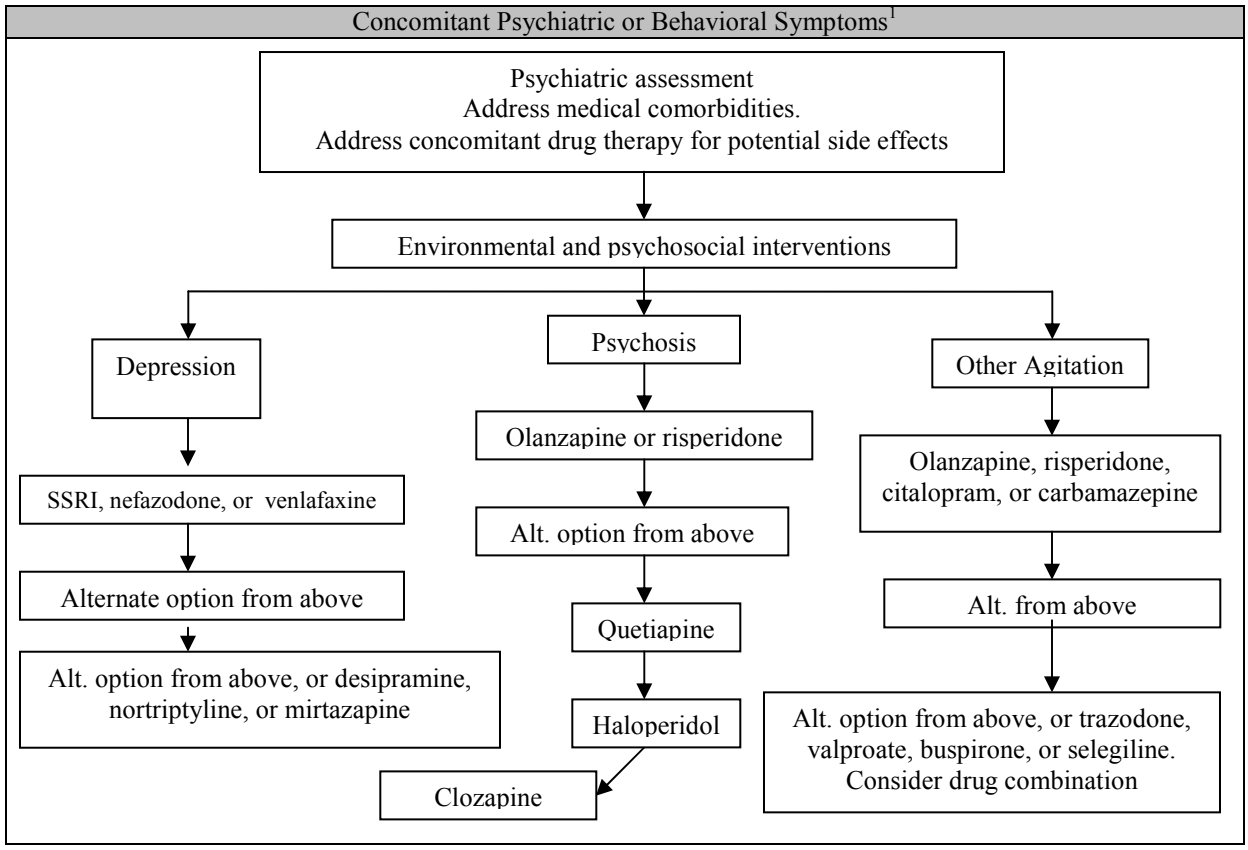
II. Evidence Based Medicine and Current Treatment Guidelines

Until recently, the cholinesterase inhibitors were the only class of drugs indicated for first-line treatment of cognitive symptoms in AD. It is believed Alzheimer's disease may be caused by a deficiency of cholinergic neurotransmission, therefore, increasing cholinergic function is likely the principal mechanism of action of the cholinesterase inhibitors. A new treatment class, N-methyl-D-aspartate (NMDA) receptor antagonists, recently became available in early 2004, with the approval of Namenda (memantine), the first drug of its kind. Because memantine is indicated for moderate to severe dementia and the cholinesterase inhibitors are indicated for mild-moderate disease, it is likely memantine will be important to AD patients who have failed treatment with cholinesterase inhibitors, or who continue to deteriorate and require combination therapy. Studies are needed in order to evaluate any benefit of memantine in earlier stages of AD and on the progression of disease.

Head-to-head trials comparing the efficacy of the cholinesterase inhibitors are limited. The Alzheimer's Association, The American Association for Geriatric Psychiatry, The American Geriatrics Society and other organizations have published treatment guidelines for the disease in hopes early and accurate diagnosis and treatment of related disorders will benefit patients. The following treatment algorithms and guidelines have been proposed.



NINCDS = National Institute of Neurological and Communicative Disorders and Stroke
ADRDA = Alzheimer's Disease and Related Disorders Association MMSE = Mini-Mental Status Exam


Concomitant Psychiatric or Behavioral Symptoms[1]
Psychiatric assessment
Address medical comorbidities.
Address concomitant drug therapy for potential side effects
Environmental and psychosocial interventions
Depression
SSRI, nefazodone, or venlafaxine
Alternate option from above
Alt. option from above, or desipramine, nortriptyline, or mirtazapine
Psychosis
Olanzapine or risperidone
Alt. option from above
Quetiapine
Haloperidol
Clozapine
Other Agitation
Olanzapine, risperidone, citalopram, or carbamazepine
Alt. from above
Alt. option from above, or trazodone, valproate, buspirone, or selegiline. Consider drug combination

Diagnosis and treatment of Alzheimer's disease and related disorders: Consensus statement of the American Association for Geriatric Psychiatry, the Alzheimer's Association, and the American Geriatrics Society.[3]

Diagnosis

Definition of dementia: The DSM-IV is a reliable definition and should be routinely used.

Criteria for establishing the diagnosis of prevalent dementing illnesses: The NINCDS-ADRDA criteria for the diagnosis of probable AD or DSM-IIIR criteria should be routinely used. Clinical criteria for Creutzfeldt-Jakob disease should be used in rapidly progressive dementia syndromes.

Practice Options:

- The Hachinski Ischemic Index may be of use in the diagnosis of cerebral vascular disease in dementia.
- The consortium for dementia with Lewy-bodies diagnostic criteria may be of use in clinical practice.
- The consensus diagnostic criteria for frontotemporal dementia may be of use in clinical practice.

Structural neuroimaging for the differential diagnosis of dementing illness:

- Structural neuroimaging with either a noncontrast CT or MR scan in the routine initial evaluation of patients with dementia is appropriate.
- Linear or columetric MR or CT measurement strategies for the diagnosis of AD are not recommended.

Genetic biomarkers for counseling patients with dementia or their families:

- Genetic testing for suspected AD is not recommended.
- Testing for tau mutation or AD gene mutations is not recommended for routine evaluation.

Management of Dementia: Pharmacologic treatment of dementia and non-cognitive behaviors of dementia, non-pharmacologic management of symptoms, and educational initiatives for families of patients with dementia

Pharmacologic treatment of Alzheimer's disease:

- Cholinesterase inhibitors should be considered in patients with mild to moderate AD, although studies suggest a small average degree of benefit.
- Vitamin E (1000I.U. PO BID) should be considered in an attempt to slow progression of AD.
- There is insufficient evidence to support the use of other antioxidants, anti-inflammatories, or other putative disease-modifying agents specifically to treat AD because of the risk of significant side effects in the absence of demonstrated benefits.
- Estrogen should not be prescribed to treat AD.
- Some patients with unspecified dementias may benefit from ginkgo biloba, but evidence-based efficacy data are lacking.

Pharmacologic treatment for noncognitive symptoms of dementia:

- Antipsychotics should be used to treat agitation or psychosis in patients with dementia where environmental manipulation fails. Atypical agents (risperidone, olanzapine, and quetiapine) may be better tolerated compared with traditional agents (haloperidol).
- Selected antidepressants (e.g. tricyclics and SSRIs) should be considered in the treatment of depression in individuals with dementia with side effect profiles guiding the choice of agent.

Educational interventions for patients with dementia and/or caregivers:

- Short-term programs directed toward educating family caregivers about AD should be offered to improve caregiver satisfaction.
- Intensive long-term education and support services should be offered to caregivers of patients with AD to delay time to nursing home placement.
- Staff of long-term care facilities should receive education about AD to reduce the use of unnecessary antipsychotics.

As part of this practice guideline, additional interventions other than education for patients and caregivers, is available for functional behaviors, problem behaviors, and care environment alterations.

III. Comparative Indications of the Alzheimer's Agents

In the early 1980s, tacrine was the first drug evaluated as a means to enhance cholinergic activity in patients with AD. Due to an extensive adverse effect profile, use of tacrine has been replaced by safer and more tolerable cholinesterase inhibitors. Tacrine is contraindicated in patients with liver disease. Donepezil has specificity for inhibition of acetylcholinesterase compared to butyrylcholinesterase, which results in fewer side effects (e.g. nausea, vomiting, and diarrhea). Rivastigmine has central activity for acetylcholinesterase and butyrylcholinesterase, with low affinity at these sites in the periphery. The last approved cholinesterase inhibitor, galantamine, also has activity as a nicotinic receptor agonist.

The cholinesterase inhibitors should be used with caution in patients with asthma, chronic obstructive pulmonary disease, sick sinus syndrome, or other supraventricular cardiac conditions. In addition, due to the mechanism of action of the cholinesterase inhibitors, gastric acid secretion may be increased as a result of increased cholinergic activity. Special caution should be used in patients at increased risk of developing ulcers or those with a history of peptic ulcer disease.

The approval of memantine (Namenda) introduces a treatment option for moderate to severe AD, for those patients who are in a more advanced stage of the disease. Not only is memantine indicated for more severe types of the disease, it is considered a N-methyl-D-aspartate (NMDA) receptor antagonist, not a cholinesterase inhibitor. Increasing evidence suggests that disturbances in glutamatergic activity play an important role in Alzheimer's disease. Memantine blocks signaling of glutamate, a neurotransmitter that plays an integral role in the neural pathways associated with learning and memory.[4] Abnormal glutamatergic activity, in addition to causing cognitive deficits, may cause neuronal toxicity thought to be involved in the destruction of brain cells in AD patients. The drug appears to inhibit abnormal glutamatergic activity and slow the cognitive, functional, and global deterioration apparent in patients with moderate to severe AD.

Table 2 summarizes the FDA-approved indications for these drugs.

Table 2. FDA-Approved Indications for the Alzheimer's Agents[5, 6]

Agent	Mild-Moderate Dementia of the Alzheimer's Type	Moderate-Severe Dementia of the Alzheimer's Type
Donepezil (Aricept)	✓	
Tacrine (Cognex)	✓	
Rivastigmine (Exelon)	✓	
Memantine (Namenda)		✓
Galantamine (Reminyl)	✓	

IV. Pharmacokinetic Parameters of the Alzheimer's Agents

The pharmacokinetic parameters for each of the agents in this class are similar with two exceptions: donepezil kinetics are not affected by food, and rivastigmine is not metabolized by the cytochrome P450 enzyme pathway.

Following oral administration, memantine is rapidly and completely absorbed in a relatively unmetabolized form from the human gastrointestinal tract.[7] Due to low protein binding, the potential for interaction with highly bound drugs, such as warfarin and digoxin, is unlikely. Memantine has little potential for drug interactions due to little metabolism and involvement with the CYP450 enzyme pathway.

Table 3 compares additional pharmacokinetic parameters for the drugs used to treat AD.

Table 3. Pharmacokinetic Parameters of the AD Agents [5, 6, 8, 9]

Agent	t_{max} (hr)	Absolute Bioavail-ability	Food Effect	Protein Binding	Metabolism	Elimination
Donepezil	3-4	100%	None	96%	Cytochrome P450 2D6 and 3A4, and glucuronidation	Elimination half-life is 70 hours; 57% renal
Tacrine	1-2	17%	Reduced bioavailability 30-40%*	55%	Cytochrome P450 1A2	First-pass effect, Elimination half-life is 2-4 hours
Rivastigmine	1	36%	t_{max} is delayed by 90 min; ↓ C_{max} by 30%; AUC ↑ by 30%	40%	Cholinesterase-mediated hydrolysis; minimal CYP450 involvement	97% Renal
Memantine	3-7	Is highly absorbed	None	42-45%	Little metabolism; CYP450 does not play a significant role	Elimination half-life is 60-80 hours; predominately renal (57%-82%)
Galantamine	1	90%	AUC is unaffected; C_{max} ↓ by 25% and t_{max} delayed by 1.5 hours	18%	Cytochrome P450 2D6 and 3A4	Elimination half-life is 7 hours; Primarily renal

*Food has no effect if tacrine is administered at least 1 hour before meals.

V. Drug Interactions with the Alzheimer' s Agents

Cholinesterase Inhibitors
Due to their mechanisms of action, all of the cholinesterase inhibitor drugs used to treat AD have the potential to interfere with the activity of anticholinergic medications. More detailed information specific to each agent is described below, followed by documented drug-interactions in Table 4. Again, since rivastigmine has minimal cytochrome P450 involvement, it may have an advantage of having less drug interactions.

Donepezil (Aricept)
Due to high protein binding with donepezil, displacement studies with other highly bound drugs such as warfarin, furosemide, and digoxin have been performed. Donepezil at concentrations of 0.3-10micrograms/ml did not affect the binding of furosemide, digoxin, or warfarin to human albumin, and similarly, the binding of donepezil to human albumin was not affected by furosemide, digoxin and warfarin. *In vitro* studies with donepezil show a slow rate of binding to the cytochrome P450 3A4 and 2D6 enzymes, indicating little likelihood of a drug interference with donepezil. It is not known whether donepezil has potential for enzyme induction.

However, it is possible that inducers of CYP2D6 and 3A4 (e.g. phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital) could increase the rate of elimination of donepezil.

Tacrine (Cognex)
Drug interactions with tacrine may occur with agents such as theophylline that undergo extensive metabolism via cytochrome P450 1A2. Many of these interactions are detailed in Table 4.

Rivastigmine (Exelon)
Based on *in vitro* studies, and because rivastigmine is metabolized by esterases rather than CYP enzymes, no drug interactions with drugs metabolized by the following isoenzymes are expected: CYP1A2, CYP2D6, CYP3A4/5, CYP2E1, CYP2C9, CYP2C8, or CYP2C19.[12] No interactions have been observed in studies between rivastigmine and digoxin, warfarin, diazepam, or fluoxetine. In addition, drugs that inhibit CYP450 metabolism are not expected to alter the metabolism of rivastigmine.

Galantamine (Reminyl)
Galantamine does not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6, or CYP2E1. This is an indicator that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low. Potential interactions exist between galantamine and cimetidine, ketoconazole, erythromycin, and paroxetine.

NMDA-Receptor Antagonists

Memantine (Namenda)
In vitro studies suggest memantine exhibits minimal inhibition of CYP450. The potential for drug interactions is very low as the drug is excreted in a mainly unmetabolized form, with low serum protein binding. In vitro investigations of the potential for interactions with memantine and donepezil, galantamine, and tacrine have demonstrated that memantine does not attenuate the inhibition of acetylcholinesterase by these drugs.[10, 11]

In vivo studies of memantine and donepezil in 24 patients, showed no clinically significant differences in the kinetics of memantine or donepezil, or in the inhibition of acetylcholinesterase by donepezil when the drugs were administered alone or in combination.[11] Because memantine is eliminated by renal tubular secretion, the interaction between memantine and triamterene / HCTZ was investigated in 20 subjects. The triamterene / HCTZ did not alter the bioavailability of memantine at steady state, and memantine did not affect the bioavailability of triamterene and its metabolite, but did cause a reduction of about 20% in the bioavailability of HCTZ.

Additionally, when administered under alkaline urine conditions, the clearance of memantine was reduced by about 80% at a urine pH of 8. Drugs that alter the pH of the urine, such as sodium bicarbonate and carbonic anhydrase inhibitors, would be expected to reduce the elimination of memantine.

In double-blind, placebo-controlled trials with memantine, 89% of patients in both treatment groups used concomitant medications during the trial.[7] No clinically meaningful differences were observed in the frequency of adverse events in patients taking memantine and concomitant medications compared with those patients not taking concomitant medications.

Table 4. Well Documented Drug Interactions with the Alzheimer's Agents[13]

Significance	Interaction	Mechanism
2 Delayed, Moderate, Suspected	Tacrine and fluvoxamine (Luvox)	Possible inhibition of tacrine metabolism (CYP1A2) by fluvoxamine resulting in elevated tacrine concentrations and increased pharmacologic and adverse effects of tacrine.
4 Delayed, Moderate, Possible	Tacrine and cimetidine	Inhibition of first-pass hepatic metabolism of tacrine may lead to elevated tacrine concentrations, increasing the pharmacologic and adverse effects. In one study, cimetidine increased the C_{max} and AUC of tacrine by 54% and 64%, respectively.
4 Delayed, Moderate, Possible	Tacrine and ibuprofen	Mechanism is unknown. Delirium was reported during concurrent administration of ibuprofen and tacrine.
4 Delayed, Moderate, Possible	Tacrine and levodopa	Possible worsening of cholinergic activity in patients with parkinsonism due to central cholinesterase inhibitor activity of tacrine, causing levodopa in patients with parkinsonism to be inhibited.
4 Delayed, Moderate, Possible	Tacrine and theophylline/aminophylline	Possible inhibition of the hepatic metabolism of theophylline, resulting in increased theophylline concentrations and toxicity.
5 Rapid, Minor, Possible	Donepezil and Antifungals (fluconazole, itraconazole, ketoconazole, and miconazole)	Azole antifungal agents may inhibit the metabolism (CYP3A4) of donepezil causing the plasma concentration of donepezil to be increased.

VI. Adverse Drug Events for the Alzheimer's Agents

Historically, about 17% of patients who receive tacrine withdraw from treatment permanently due to adverse events.[9] Transaminase elevations were the most common reason for withdrawals, accounting for 8% of all tacrine-treated patients. Transaminase elevations occur infrequently with the other Alzheimer's agents. For this reason, tacrine use is disadvantageous compared to the other agents in this class. Gastrointestinal (GI) adverse events occur most frequently among the cholinesterase inhibitor agents. The mechanism of action of donepezil (specificity for acetylcholinesterase) may result in lower GI adverse events compared to the other agents. Table 5 illustrates the common adverse events reported for the cholinesterase inhibitors.

Table 5. Common Adverse Events (%) Reported for the Cholinesterase Inhibitors[1]

Adverse Event	Donepezil	Tacrine	Rivastigmine	Galantamine
Elevated liver function tests	NR	29%	NR	NR
Nausea and vomiting	NR	28%	NR	NR
Nausea	11%	NR	47%	24%
Vomiting	5%	NR	31%	13%
Diarrhea	10%	16%	19%	9%
Headache	10%	11%	17%	8%
Dizziness	8%	12%	21%	9%
Muscle cramps	6%	9%	NR	NR
Insomnia	9%	6%	9%	5%
Fatigue	5%	4%	9%	5%
Anorexia	4%	9%	17%	9%
Depression	3%	4%	6%	7%
Abnormal dreams	3%	NR	NR	NR
Weight increase	3%	3%	3%	7%
Somnolence	2%	4%	5%	4%
Abdominal pain	NR	8%	13%	5%
Tremor	NR	2%	4%	3%
Agitation	NR	7%	NR	NR
Rhinitis	NR	8%	NR	NR

NR = Incidence not reported

In double-blind, placebo-controlled dementia trials (940 memantine-treated patients, 922 placebo-treated patients) 1,286 patients reported treatment-emergent adverse events. A comparable number of placebo-treated patients (624) and memantine-treated patients (662) reported a treatment-emergent adverse event.[7] Most treatment-emergent adverse events were considered mild or moderate in severity and not related to the trial drug.

Dizziness, confusion, headache, and constipation were reported in greater than 5% of memantine patients and at an incidence greater than placebo, while agitation, fall, and accidental injury occurred in greater than 5% of placebo patients at an incidence greater than memantine.[6] Treatment-emergent adverse events occurring in ≥ 5% of either placebo or memantine treated patients are shown in Table 6. The number of treatment-emergent adverse events did not vary by dementia diagnosis or severity and events were similar between treatment groups. The incidence of serious adverse events did not vary between placebo-treated patients and memantine-treated patients (14.6% vs. 13.5%, respectively).

Table 6. Treatment-Emergent Adverse Events in ≥ 5% of Patients[6, 7, 9]

Adverse Event	Placebo (n=922) n (%)	Memantine (n=940) n (%)
Dizziness	49 (5.3)	64 (6.8)
Agitation	98 (10.6)	63 (6.7)
Confusion	42 (4.6)	58 (6.2)
Headache	31 (3.4)	54 (5.7)
Constipation	28 (3.0)	50 (5.3)
Fall	50 (5.4)	48(5.1)
Accidental Injury	64 (6.9)	44 (4.7)

Discontinuations

Adverse events were the most common reason for discontinuation of memantine in pre-marketing trials (11.5% placebo vs. 10.1% memantine). In one double-blind, placebo-controlled trial, memantine was administered in combination with donepezil; the addition of memantine resulted in substantially fewer discontinuations due to any adverse event (7.4%) compared to donepezil and placebo treatment.[14] In four open-label extension studies, discontinuation due to any adverse event was similar between treatment groups (9.8% placebo-memantine, 11.6% memantine-memantine).

VII. Dosing and Administration of the Alzheimer's Agents

In looking at dosing of the Alzheimer's agents, donepezil is the only agent approved for once daily dosing with no titration (rivastigmine and galantamine require titration), while both rivastigmine and galantamine are the only available agents in a liquid dosage form. Although studies indicate the clearance of donepezil and rivastigmine may be altered in renal and hepatic impairment, both manufacturers have not provided specific recommendations for dosing in patients with renal or hepatic disease. Galantamine use is not recommended in patients with severe hepatic or renal impairment, and caution should be used when the drug is given to patients with moderate hepatic or renal disease. Tacrine should be used with caution in patients with pre-existing liver disease, and in renal impairment, especially in the event of electrolyte disturbances from adverse GI events. When given with food, the GI tolerability of the cholinesterase inhibitors may be improved.

Table 7 further describes the dosing regimens for the agents in this review.

Table 7. Dosing for the Alzheimer's Drugs[1, 5, 6, 8, 9]

Agent	Availability	Dose /Frequency/Duration
Donepezil	5mg and 10mg Tablets	Starting: 5mg QHS, with or without food Maintenance: 5-10mg QD Time between dosage adjustment: 4-6 weeks
Tacrine	10mg, 20mg, 30mg, and 40mg Capsules	Starting: 10mg QID at least 1 hour before meals Maintenance: 20-40mg QID Time between dosage adjustment: 4-6 weeks
Rivastigmine	1.5mg, 3mg, 4.5mg, 6mg Capsules and Oral solution 2mg/ml	Starting: 1.5mg BID with the morning and meals Maintenance: 3-6mg BID Time between dosage adjustment: 2 weeks
Memantine	5mg and 10mg tablets, 4 week titration pak	Week 1: 5mg QD Week 2: 10mg/day (5mg BID) Week 3: 15mg/day (10mg QAM, 5mg QPM) Week 4: Maintenance dose-20mg/day (10mg BID)
Galantamine	4mg, 8mg, and 12mg Tablets and Oral solution 4mg/ml	Starting: 4mg BID with the morning and evening meals Maintenance: 8-16mg BID Time between dosage adjustment: 4 weeks

Special Dosing Considerations

Renal and Hepatic Insufficiency:

- There are no specific manufacturers recommendations for dosing adjustments with donepezil in patients who have renal or hepatic insufficiency.
- Galantamine is not recommended in patients with severe hepatic or renal impairment and caution is recommended for patients with moderate hepatic or renal disease.
- Dosing adjustments with rivastigmine are not necessary in hepatic disease or renal disease as the drug is individually titrated to tolerability.
- Tacrine should be used with extreme caution in patients with hepatic and renal impairment.
- Memantine: In patients with moderate renal impairment, dosage reduction should be considered with memantine. Use of memantine in severe renal impairment has not been evaluated and is not recommended. The kinetics of memantine in patients with hepatic impairment have not been investigated, but would be expected to be only modestly affected.[6, 8]

Other:

- While galantamine and rivastigmine are available in oral solution formulations, donepezil and memantine are both film-coated tablets. No data is available on the safety of crushing donepezil or memantine for administration.
- Memantine can be taken with or without food.

VIII. Comparative Effectiveness of the Alzheimer's Agents

Until recently, there were no head-to-head trials comparing the efficacy of the cholinesterase inhibitors in Alzheimer's disease. Limited comparative data is now available. As memantine is the only NMDA receptor antagonist, comparative data is not available, however, memantine has been studied in combination with donepezil. Memantine has been studied in Europe during the last decade for the treatment of dementia, and it was approved in the European Union in May of 2002 for the treatment of moderately severe to severe AD. In the U.S., the completion of two large Phase III clinical trials confirmed earlier European findings that memantine is effective for the treatment of moderate to severe AD. There are a small number of efficacy trials available for memantine. FDA approval was granted based on data from limited placebo-controlled studies.

A large proportion of patients experience lack or loss of therapeutic benefit from an initial agent, or discontinue treatment due to safety or tolerability issues. Often, no alternative treatment is offered once an initial agent has been stopped, thus the treatment duration is short in comparison with the chronic nature of the disease. A number of studies have evaluated the effect of switching from donepezil to rivastigmine. Studies indicate that approximately 50% of patients who experience lack or loss of efficacy with donepezil respond to treatment with rivastigmine.[15] The same studies also indicated that safety and tolerability problems with donepezil were not predictive of similar problems with rivastigmine.

Table 8 illustrates important efficacy trials for the Alzheimer's drugs.

Table 8. Additional Outcomes Evidence for the AD Drugs

Study	Sample	Duration	Results
Donepezil vs. rivastigmine[16]	n=111	12 week multinational, randomized study	In comparing the tolerability and cognitive effects of donepezil (up to 10mg QD) and rivastigmine (up to 6mg BID) in patients with mild-moderate Alzheimer's disease: • More patients taking donepezil completed the study (89.3%) compared to the rivastigmine group (69.1%) P=0.009. • 10.7% of the donepezil group and 21.8% of the rivastigmine group discontinued treatment due to adverse events. • 87.5% of the donepezil patients and 47.3% of the rivastigmine patients remained on the maximum approved dose of each drug at the last study visit. • Both groups showed comparable improvements in the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) administered at weeks 4 and 12.
Galantamine vs. donepezil[17]	n=182	52 week randomized, parallel-group, multicenter study	When evaluating the long-term efficacy and safety of galantamine 24mg/day and donepezil 10mg/day in patients with Alzheimer's disease: • The Bristol Activities of Daily Living Scale total score showed no significant difference between treatment groups in mean change from baseline to week 52. • In terms of cognition, galantamine patients' scores on the MMSE at week 52 did not differ significantly from baseline, whereas donepezil patients' scores deteriorated significantly from baseline (P<0.0005). • The between group difference in MMSE change, which showed a trend for superiority of galantamine, did not reach statistical significance. • In the ADAS-cog analysis, between group differences for the total population were not significant, whereas galantamine treated patients with MMSE scores of 12-18 demonstrated an increase (worsening) in the ADAS-cog score of 1.61 +/- 0.80 versus baseline, compared with an increase of 4.08 +/- 0.84 for patients treated with donepezil. • More caregivers of patients receiving galantamine reported reductions in burden compared with donepezil.

			• Changes from baseline in Neuropsychiatric Inventory were similar for both treatments.
Donepezil vs. galantamine[18]	n=120	12 week randomized, multinational study	In comparing the ease of use and tolerability of donepezil (up to 10mg QD) and galantamine (up to 12mg BID), and to investigate the effects of both treatments on cognition and activities of daily living: • Physicians and caregivers reported greater ease of use with donepezil compared to galantamine at weeks 4 and 12. • Significantly greater improvements in cognition were observed for donepezil versus galantamine on the ADAS-cog at week 12 and at endpoint. • Activities of daily living improved significantly in the donepezil group compared with the galantamine group at weeks 4 and 12 (P<0.05). • 46% of galantamine patients reported GI adverse events versus 25% of donepezil patients.
Rivastigmine in moderately severe AD[19]	n=2,126	Retrospective pooled analysis from 3 randomized, placebo-controlled, double-blind, 6 month trials	In evaluating the effectiveness of rivastigmine in more severe Dementia: • Mean ADAS-cog score declined by 6.3 points in the placebo group and increased by 0.2 points in the rivastigmine group (P<0.001). • Clinical benefits were also observed with the MMSE, the six-item progressive deterioration scale, and items of the BEHAV-AD assessed efficacy. • Exelon showed the same pattern of adverse events as in other studies, but the relative risk of dropping out due to adverse events was lower than in subjects with milder AD.
Effects of galantamine on caregiver distress and behavioral disturbances[20]	n=978	21 week randomized, placebo-controlled study	When evaluating the impact of galantamine on the pattern and evolution of behavioral disturbances in patients with mild-moderate AD, and in looking at caregiver distress related to patients' behavior: • Neuropsychiatric inventory scores worsened with placebo, whereas patients treated with 16 or 24mg/day of galantamine had no change in total neuropsychiatric inventory scores. • Behavioral improvement in patients symptomatic at baseline ranged from 29% to 48%-changes were evident in patients receiving 16 and 24mg/day of galantamine. • High dose galantamine was associated with a significant reduction in caregiver distress.
Galantamine benefits sustained for 36 months[21]	n=194	36 month randomized, double-blind, placebo-controlled trial	To report the long-term cognitive effects of galantamine given continuously for 36 months in mild-moderate AD patients: • Patients treated continuously with galantamine for 36 months increased a mean +/- SE of 10.2 +/- 0.9 points on the AD assessment scale-11-item cognition subscale. This was a substantially smaller cognitive decline (approximately 50%) than that predicted for the placebo group. • Patients discontinuing galantamine therapy before 36 months had declined at a similar rate before discontinuation as those completing 36 months of treatment. • Almost 80% of patients who received galantamine for 36 months seemed to demonstrate cognitive benefits compared with those predicted for untreated patients.
Memantine and donepezil in moderate to severe AD[22]	n=404	24 week double-blind, placebo-controlled U.S. trial	In evaluating the functional, cognitive, and global outcome measures in moderate to severe AD patients receiving ongoing donepezil therapy for at least 6 months, who were given memantine 10mg BID or placebo: • A significantly greater therapeutic effect was observed in the memantine group than in the placebo group on the ADCS-ADL, SIB, and CIBIC-Plus. • Patients receiving memantine in combination with donepezil demonstrated significantly less decline in ADCS-ADL scores compared to patients receiving donepezil/placebo over the 24-week study period

			(p=0.02). • Patients receiving memantine showed significantly less cognitive decline in SIB scores compared to patients receiving placebo. In fact, therapy with memantine/donepezil resulted in sustained cognitive performance above baseline compared with the progressive decline seen with the donepezil/placebo treatment. • The change in total mean scores favored memantine vs. placebo for the CIBIC-Plus (possible score range, 1-7), 4.41 (0.074) vs. 4.66 (0.075), respectively (p=0.03). • Treatment discontinuations due to adverse events for memantine vs. placebo were 15 (7.4%) vs. 25 (12.4%), respectively.
Efficacy and safety of donepezil[23]	n=1,113	12 week, open label, multicenter trial	In evaluating the efficacy, tolerability, and safety of donepezil in mild-moderate Alzheimer's disease: • Out of 1,113 patients, 88.9% of patients completed the study and 5% of patients discontinued treatment because of adverse events. • Donepezil significantly improved cognition compared to baseline, at 4 and 12 weeks. • The mean change from baseline MMSE score at week 12 was +1.73 +/- 0.10. • Donepezil was associated with significant improvements in patient social interaction, engagement and interest, and initiation of pleasurable activities at all weekly assessments and at week 12 (P<0.0001). • Donepezil was well tolerated.
Galantamine vs. placebo on sleep related outcomes in AD[24]	n=261	3 month, double-blind, flexible-dose trial of galantamine vs. placebo	In assessing the effect of galantamine on sleep quality in patients with mild-moderate AD: • There were no significant differences between groups on the Pittsburgh sleep quality index total or subscales. • There was no difference found on the neuropsychiatric inventory sleep score at month 3.
Donepezil and Vitamin E[25]	n=130	1 year retrospective chart review	In order to examine the long-term effects of combination donepezil and vitamin E therapy on patients with AD, a retrospective chart review was performed. Data were compared with the Consortium to Establish a Registry for Alzheimer's Disease database for patients collected prior to the availability of these treatment options. • Patients declined at a significantly lower rate as compared with the Consortium to Establish a Registry for Alzheimer's Disease data. • The long-term combination therapy of donepezil and vitamin E appears beneficial for patients with Alzheimer disease. • Future prospective studies would be needed to compare combination treatment to vitamin E and donepezil alone.
Donepezil delays nursing home placement[26]	n=1,115	Follow-up of patients previously enrolled in one of three randomized, double-blind, placebo-controlled trials of donepezil, and two subsequent open-label studies.	Data was obtained through interviews with caregivers and through chart reviews of patients previously enrolled in donepezil studies: • Use of donepezil of 5mg/day or more was associated with significant delays in nursing home placement. • A cumulative dose-response relationship was observed between longer-term sustained donepezil use and delay of nursing home placement. • When donepezil was taken at effective doses for at least 9-12 months, conservative estimates of the time gained before nursing home placement were 21.4 months for first-dementia-related nursing home placement and 17.5 months for permanent nursing home placement.

Tacrine Study Group[27]	n=468	12 week double-blind, placebo-controlled, parallel-group study	In comparing the efficacy and safety of tacrine with placebo in patients with AD: • After 12 weeks, dose-related improvement was significant on the ADAS cognitive component (P=0.014), clinician-rated Clinician Global Impression Change (CGIC) (P=0.016), and caregiver-rated CGIC (P=0.028) for patients given tacrine. • Among patients receiving 80mg/day of tacrine, 51% achieved a four-point or greater improvement of the ADAS cognitive component after 12 weeks of treatment. • Reversible asymptomatic transaminase elevations greater than three times of normal occurred in 25% of patients. • Other treatment related adverse events included nausea and/or vomiting (8%), diarrhea (5%), abdominal pain (4%), dyspepsia (3%), and rash (3%).
28-week U.S. Trial: memantine vs. placebo[28]	n=252	28 week double-blind treatment study	In evaluating functional, cognitive, and global outcome measures in patients with moderate to severe AD who received either memantine 10mg BID or placebo: • A significantly greater effect was observed in the memantine group compared to the placebo group on the ADCS-ADL and SIB. • Memantine patients showed significantly less cognitive decline on the SIB total score compared to placebo-treated patients over the 28-week study period (p=0.002). • There was a significant difference in favor of memantine at week 28 on the CIBIC-Plus using the observed-cases analysis (mean score: 4.74 placebo vs. 4.38 memantine, p=0.025), and a numerical difference at study endpoint in favor of memantine using the last-observed-carried-forward analysis (mean score: 4.73 placebo vs. 4.48 memantine, p=0.064). • Memantine-treated patients showed significantly less functional decline compared to placebo-treated patients over the 28-week study period.
12-week memantine Latvia trial: Results of the 9M-Best Study[29]	n=166	12 week double-blind, placebo-controlled study	In determining any benefit of memantine when administered to patients with severe dementia, either AD or vascular dementia, by studying functional and global efficacy measures: • Significantly greater improvement was observed in the memantine group compared to the placebo group on the BGP-care dependency subscale and the CGI-C. • Separate analyses of the AD population alone also yielded statistically significant results in favor of patients receiving memantine, by either the last-observed-carried-forward analysis or the observed-cases analysis on both outcome measures. • At study endpoint, memantine patients showed significantly greater functional improvement compared to patients who received placebo, at study endpoint (p=0.012).
Memantine for vascular dementia[30]	n=321	28 week double-blind, placebo-controlled study	In order to examine the efficacy and tolerability of memantine in the treatment of mild to moderate vascular dementia, patients were randomized to receive 10mg memantine or placebo twice daily: • After 28 weeks, the mean ADAS-cog scores were significantly improved relative to placebo. • In the intention-to-treat population, the memantine

			group mean score had gained an average of 0.4 points, whereas the placebo group mean score had declined by 1.6 points. • The response rate for CIBIC-plus, defined as improved or stable, was 60% with memantine compared with 52% with placebo (p=0.227). • Among the secondary efficacy parameters, the MMSE was significantly improved with memantine compared to deterioration with placebo (p=0.003). • The Gottfries-Brane-Steen Scale intellectual function subscore and the Nurses' Observation Scale for Geriatric Patients disturbing behavior dimension also showed differences in favor of memantine (p=0.04 and p=0.07), respectively.
Memantine for vascular dementia[31]	n=579	28 week double-blind, placebo-controlled study	In evaluating the safety and efficacy of memantine 20mg daily vs. placebo in mild to moderate vascular dementia: • At endpoint, memantine was shown to improve cognition relative to placebo in this population. • The change of ADAS-cog from baseline differed by a mean of –1.75 points (95% confidence intervals –3.023 to –0.49) and a median of 2 points between the two groups. • The CGI-C ratings showed no significant differences between treatment groups. • A total of 77% of all memantine-treated patients experienced an adverse event, versus 75% of the placebo-treated patients. Dizziness was the most frequent adverse event (11% vs. 8%, respectively).
Long-term donepezil treatment[32]	n=565	12 week run-in period study; 156 weeks total duration	In evaluating donepezil's ability to produce worthwhile improvements in disability, dependency, behavioral and psychological symptoms, caregiver psychological wellbeing, or delay in institutionalization: • Cognition averaged 0.8MMSE points better (95% CI 0.5-1.2;p<0.0001) and functionality 1.0 BADLS points better (0.5-1.6;p<0.0001) with donepezil over the first 2 years. • No significant benefits were seen with donepezil compared with placebo in institutionalization (42% vs. 44% at 3 years; p=0.4) or progression of disability (58% vs. 59% at 3 years; p=0.4). • The relative risk of entering institutional care in the donepezil group compared with placebo was 0.97 (95% CI 0.72-1.30; p=0.8); the relative risk of progression of disability or entering institutional care was 0.96 (95% CI 0.74-1.24; p=0.7). • Similarly, no significant differences were seen between donepezil and placebo in behavioral and psychological symptoms, caregiver psychopathology, formal care costs, unpaid caregiver time, adverse events or deaths, or between 5 mg and 10 mg donepezil. • Conclusion: Donepezil offers benefits below minimally relevant thresholds. More effective treatments than cholinesterase inhibitors are needed for Alzheimer's disease.

Staging Tools Key:
CGI-S: Clinical Global Impression of Severity Scale
CHI-C: Clinical Global Impression of Change Scale
GDS: Global Deterioration Scale
FAST: Functional Assessment Staging Tool

Cognition Efficacy Measures Key:
SIB: Severe Impairment Battery
CIBIC-Plus: Clinician's interview-Based impression of Change Plus Caregiver Input
ADCS-ADL: Alzheimer's Disease Assessment Scale Cognitive Subscale
BGP: Behavioral Rating Scale for Geriatric Patients
MMSE: Mini-Mental Status Exam

Additional Evidence

Dose Simplification: Little evidence is available on medication adherence in Alzheimer's Disease. One study that looked at pharmacy claims data suggests the probability of a new user continuing donepezil at 90 days was 0.797 +/- 0.103 and at 180 days was 0.627 +/- 0.124.[33] Additionally, 13.9% of those who continued therapy for at least 180 days showed gaps in treatment of six weeks or more.
A literature search of Medline/Pubmed and Ovid did not reveal additional adherence studies specific to, or comparing the Alzheimer's agents.

Stable Therapy: Cholinesterase inhibitors are associated with nausea and vomiting ranging from 5% to 31%, mostly occurring during the initiation/titration phase of therapy. Additive risk of adverse events may be expected with coadministration of these drugs, or with inadequate washout periods between agents. One report of fatal aspiration pneumonia has been published after initiation of rivastigmine and discontinuation of donepezil with no washout period between therapies.[34] A washout period should be considered, and is usually recommended when switching between cholinesterase inhibitors. No studies evaluating the direct effect of switching Alzheimer's treatments, on cognitive function, are available.

The pharmacological differences among the cholinesterase inhibitors and evidence from comparative studies support a switch strategy when a patient is intolerant to one drug or when a therapeutic dose to one drug cannot be reached.[35] As previously mentioned, one study reported that when switched from donepezil to rivastigmine, about 50% of those who had side-effects or no efficacy with donepezil tolerated or responded well to rivastigmine. In about a third of patients treated with a cholinesterase inhibitor, symptoms will worsen in the first 6 months of initial treatment, and the responsiveness to a second inhibitor is variable.

A post-hoc analysis of a 5-month trial with galantamine showed that patients had similar efficacy outcomes, whether or not they had received prior anticholinesterase therapy, suggesting that a previous failure to respond to another cholinesterase inhibitor did not predict response to galantamine.[36] On the basis of available data, it is suggested that patients not tolerating or not responding to one particular cholinesterase inhibitor may still draw benefits upon switching to another.

There is only limited guidance in the literature on the safety of switching the cholinesterase inhibitors. The maintenance of a therapeutic inhibition of acetylcholinesterase throughout the switching period is desirable and, for both galantamine and rivastigmine, time is needed to reach a therapeutic dose after the start of the titration. More research is needed to establish practice guidelines for switching cholinesterase inhibitors.

Maelicke has suggested the following on switching from donepezil to galantamine. His work has suggested donepezil is completely eliminated after 15 days, and a switch to galantamine should consider the rate of dose escalation after 4 weeks.[37] He also

postulated that galantamine does not cause any long-lived increases in the acetylcholinesterase inhibition produced by the first drug used. Preliminary findings suggest there does not seem to be an urgent need for a washout protocol. This means the same dose escalation profile used for first-time galantamine patients could be used for patients who were exposed previously to other cholinesterase inhibitors. Because the effects of galantamine are rapidly reversible, switching from a previously used cholinesterase inhibitor to galantamine should be easy. The most conservative switch protocols (for use if adverse events occur) suggest a 1 week washout, followed by a daily dose of galantamine 8mg (4mg BID) escalated to 16mg QD (8mg BID) after 4 weeks.

Impact on Physician Visits: Data is not available relating to Alzheimer's treatments and impact on utilization of physician services. However, some literature is available on Alzheimer's disease and utilization of services. One study by Fillenbaum, et al. looked at the probability and frequency of outpatient visits of patients with Alzheimer's disease.[38] In the Medicare population, the number of patients with AD and a Medicare-reimbursed outpatient visit ranged from 81% to 95% and was not related to stage of dementia or institutional status. Another study showed the onset of AD is not associated with greater use of acute care services nor is the high use of nursing home care offset by fewer ER or hospital encounters.[39] A study evaluated a care consultation multi-component telephone intervention program where healthcare professionals work with patients and caregivers to determine resources within the family of an Alzheimer's patient.[40] Alzheimer's patients in the program felt less embarrassed and isolated because of their memory problems and reported less problems coping with their disease. Intervention patients with more severe impairment had fewer physician visits, were less likely to have an emergency room visit or hospital admission, and had decreased depression and strain.

IX. Conclusions

All four of the cholinesterase inhibitors have the same FDA approved indication for Alzheimer's disease. A review of the pharmacokinetic properties of each agent shows donepezil (Aricept) kinetics are not affected by food, and rivastigmine (Exelon) is the single agent not metabolized by the cytochrome P450 enzyme system, resulting in less potential for drug interaction. Above all, use of tacrine (Cognex) is associated with high rates of liver transaminase level elevations, making it the cholinesterase inhibitor at a significant disadvantage due to adverse events.

With regards to dosing, donepezil is the only cholinesterase inhibitor dosed once daily with no dosing titration, and is the only drug studied in combination with memantine (Namenda). In addition, clinical data from trials listed above suggest donepezil is better tolerated than rivastigmine or galantamine. However, only galantamine and rivastigmine are available in an oral liquid formulation. Efficacy data on cognitive function from trials comparing the cholinesterase inhibitors is mixed. More head-to-head studies are needed between these agents to fully evaluate their efficacy. Currently, the agents in this class (excluding tacrine) remain comparable in efficacy, and important in the treatment of Alzheimer's disease.

A significant amount of literature supports use of the cholinesterase inhibitors as first-line agents for mild-moderate AD. However, as there are no drugs commonly used for their effectiveness in moderate-to-severe AD, the small benefit offered by memantine may be beneficial for some patients who have tried and failed cholinesterase inhibitors or whose cognitive disease continues to progress. Until more efficacy data becomes available, memantine should be reserved for those patients who have not responded to other first-line agents (cholinesterase inhibitors) for AD.

Therefore, donepezil, rivastigmine, and galantamine offer significant clinical advantage in general use but are comparable to each other. Additionally, tacrine (Cognex®) possesses an extensive adverse effect profile.

X. Recommendations

Alabama Medicaid should work with the manufacturers of the brands of donepezil, rivastigmine, and galantamine, on cost proposals so that at least one brand cholinesterase inhibitor is placed in preferred status. No brand of memantine is recommended for preferred status. Brand products of tacrine (Cognex®) should not be placed in preferred status regardless of cost.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Proton Pump Inhibitors
AHFS 562836
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I. Overview

Proton pump inhibitors (PPIs) are widely used to treat a variety of acid-related gastrointestinal disorders including gastroesophageal reflux disease (GERD), peptic ulcer disease (PUD), NSAID-induced gastropathy, and hypersecretory conditions such as Zollinger-Ellison syndrome. In a report of the top 200 drugs of 2002, all five proton pump inhibitors ranked among the top 30 drugs.[1]

GERD is a common medical condition estimated to affect about 10% of the U.S. population. The most common symptoms of uncomplicated GERD include heartburn and regurgitation. Symptom severity often does not correlate with the extent of esophageal damage, and the majority of patients have nonerosive disease.[2-3] GERD is associated with increased risk of adenocarcinoma of the esophagus, as well as the precursor lesion, Barrett's esophagus. However, the absolute risk of cancer is low.[4] PPIs are a mainstay of therapy for GERD, particularly for moderate to severe cases.

The two most widely recognized causal factors in the development of peptic ulcers are the presence of the *H. pylori* organism and the use of NSAIDs, including low-dose aspirin for cardiovascular protection. Gastrointestinal problems are the most common side effects associated with NSAID use. Approximately 15% of NSAID users will have dyspepsia and 1-4% will have significant GI complications each year (e.g. perforated ulcers or GI bleeding requiring hospitalization).[5] Another rare cause of PUD is Zollinger-Ellison syndrome. This syndrome is characterized by gastric acid hypersecretion, severe peptic ulcer disease, and tumors of the non-beta islet cells of the pancreas.[6] PPIs play a role in the treatment and prevention of peptic ulcers due to NSAID-induced gastropathy and hypersecretion syndromes, and as part of combination therapies to eradicate the *H. pylori* organism.

Proton pump inhibitors exert their therapeutic effects by suppressing gastric acid secretion. The PPIs are substituted benzimidazoles and specifically inhibit the H^+/K^+-ATPase enzyme system (regarded as the acid or proton pump) within the gastric parietal cell.[7] Since they affect the final step in the acid production pathway, PPIs are generally more effective agents at suppressing acid secretion, and provide superior healing rates and symptom relief, than H2 receptor antagonists or antacids. While there are some pharmacokinetic and drug-drug interaction differences exist between agents, overall the agents are very similar in terms of efficacy and safety profile.

There are currently five proton pump inhibitors (PPIs) available on the market and included in this review. Table 1 lists the available products and their brand and generic names. Omeprazole powder for oral suspension (Rapinex) will be reviewed at a future time. This review encompasses all dosage forms and strengths. Only omeprazole is available as a generic.

Table 1. Proton Pump Inhibitors in this Review

Generic Name	Formulation	Example Brand Name
Esomeprazole magnesium	Oral capsules	Nexium
Lansoprazole	Oral capsules, suspension, and disintegrating tablets	Prevacid
Omeprazole	Oral capsules (prescription) and tablets (OTC)	Prilosec**
Omeprazole	Powder for oral suspension (immediate-release)	Rapinex†
Pantoprazole sodium	Oral tablets and intravenous injection	Protonix
Rabeprazole sodium	Oral tablets	Aciphex

*Most formulations except pantoprazole IV are delayed-release; all are available prescription-only except OTC (over-the-counter) omeprazole tablets.
**Available generically (10 and 20mg only).
†Omeprazole powder for oral suspension (Rapinex) was FDA approved in May 2004. The product launch is expected in the fourth quarter 2004. Per Alabama Medicaid P&T policy, this omeprazole product is eligible for review after it has been commercially available for at least 6 months. Omeprazole powder for oral suspension will be reviewed at a future time.

II. Current Treatment Guidelines

Gastroesophageal Reflux Disease (GERD)[2-4,8-11]

Treatment of GERD is driven by the severity of symptoms and presence or absence of esophageal lesions. Patients with erosive esophagitis and/or moderate to severe symptoms should be treated with a PPI as the drug of choice. PPIs are the most effective agents for acute healing and symptom relief.[12-14] Additionally, approximately 50-80% of patients with esophagitis will have recurrence of disease within 6-12 months after discontinuing therapy. These patients usually require maintenance therapy, and treatment with a PPI is often required. Some patients initially requiring multiple doses per day of PPI for symptom relief may be able to "step-down" to once daily PPI dosing.[15] Nocturnal acid breakthrough may still occur in many patients receiving even twice-daily PPI therapy. Several small studies advocate the use of combination therapy with an H_2RA dose added at bedtime to the existing PPI dosing regimen (PPI before breakfast and supper). The data for this treatment regimen is conflicting and needs to be validated in large-scale trials.[16-20]

Typically, the approach to patients with mild GERD symptoms includes lifestyle modifications and over-the-counter (OTC) medications as needed (e.g. antacids and OTC H_2 receptor antagonists [H_2RAs]). If these measures are not successful, drug therapy can be "stepped-up" to twice-daily prescription H_2RAs or a PPI may be started. Promotility agents may also be used, though their use in GERD may be limited to combination therapy with an acid-reducing agent for patients with delayed gastric emptying. Because some patients with mild GERD symptoms may go into remission after a single course of therapy, a trial off medication after 6-8 weeks of therapy may identify those patients not requiring chronic maintenance therapy.

There is also increasing interest in the use of intermittent courses of therapy (e.g. 2-4 week treatment courses when symptoms flare) as well as "on-demand" therapy (day-to-day) with both PPIs and H2RAs.[8-9,21] These treatment approaches have shown efficacy and may be rational regimens in some patients with mild disease. However, the role of these two treatment modalities remains to be established.

Peptic Ulcer Disease (PUD)

The two most common causes of PUD are infection with the *H. pylori* organism and NSAID use. Appropriate antibiotic therapy of *H. pylori* can eradicate the organism, facilitate ulcer healing and decrease ulcer recurrence in many patients with uncomplicated PUD. Curing the disease provides the opportunity to discontinue chronic antisecretory regimens with the attendant risks of drug-drug interactions, adverse effects and typically expensive therapy. However, there is evidence that the proportion of non-*H. pylori* ulcers is increasing. In many cases, the etiology may be related to NSAID use, especially with the availability of over-the-counter NSAIDs, but cases of idiopathic PUD may also occur.[22] If a cause cannot be identified, idiopathic ulcers are generally treated with traditional PUD doses of PPI or H2RA for 4-8 weeks, depending on the selected agent. Patients with recurrent or refractory ulcers may require longer treatment durations or maintenance therapy.

***H. Pylori* Positive PUD**

Guidelines for the treatment of PUD were formulated by the American College of Gastroenterology (ACG) and formally published in 1996.[23] Updated guidelines for treatment of *H. pylori* infection were published in 1998.[24] Testing for *H. pylori* infection and eradication following treatment have improved with the introduction of less invasive, accurate tests such as the urea breath and the stool antigen tests. The guidelines emphasize the need to treat all *H. pylori* infected PUD patients with an appropriate antibiotic drug regimen, and recommend target eradication rates of $\geq$90% on per-protocol analysis or $\geq$80% on intent-to-treat analysis for antibiotic regimens. The most commonly used regimens include triple therapy with a proton pump inhibitor plus either amoxicillin and clarithromycin or metronidazole and clarithromycin.

Treatment failure is often associated with poor patient compliance or antimicrobial resistance. Drug resistance is most common with metronidazole and clarithromycin. Resistance to amoxicillin and tetracycline is uncommon. Ideal duration of therapy remains controversial, with most European countries utilizing 7 day courses of therapy, while in the U.S., 10-14 day courses of therapy are FDA approved. For second-line therapy, treatment with PPI-based triple therapy utilizing a different antimicrobial regimen is recommended, or quadruple therapy involving a PPI or H2RA plus bismuth-based triple regimen with high dose metronidazole can be used.[25-26]

Nonsteroidal Anti-inflammatory Drug (NSAID)-Induced PUD[27-28]

NSAID use is an important factor in ulcer development and healing, particularly in those patients with refractory ulcers. Several factors have been identified that place NSAID-using patients at increased risk of GI complications. These include a history of ulcer or GI hemorrhage, increased age (defined as anywhere from >60 years to >75 years of age), high dosage of NSAID or use of multiple NSAIDs, and concurrent use of corticosteroids or anticoagulants.

Preventive therapy with misoprostol or a PPI should be considered for patients at high risk of GI complications while receiving NSAID therapy. H_2RAs may not prevent gastric ulcers and are not usually recommended for NSAID-induced ulcer prophylaxis. Treatment of existing NSAID-induced ulcer disease may consist of any approved therapy, including *H. pylori* eradication if applicable. NSAIDs should be discontinued when possible if a patient develops ulcer disease, and treatment with a PPI is recommended if patients must continue NSAID therapy in the presence of PUD.

III. Indications of the Proton Pump Inhibitors[29-34]

Table 2. Indications for the PPIs

Indication	Esomeprazole	Lansoprazole	Omeprazole	Pantopra
Gastroesophageal Reflux Disease				
Healing of erosive esophagitis	✓	✓	✓	✓
Maintenance of healing of erosive esophagitis	✓	✓	✓	✓
Treatment of symptomatic GERD	✓	✓	✓	
Peptic Ulcer Disease				
Helicobacter pylori eradication to reduce the risk of duodenal ulcer recurrence	✓[2]	✓[3]	✓[4]	
Healing of duodenal ulcers		✓	✓	
Maintenance of healed duodenal ulcers		✓		
Treatment of active, benign gastric ulcer		✓	✓	
Healing of and risk reduction for NSAID-associated gastric ulcer		✓		
Other				
Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome		✓	✓	✓

[1]The IV formulation of pantoprazole is indicated for both the treatment of pathological hypersecretory conditions, as well as for treatment of GERD associated with a history of erosive esophagitis for 7-10 days, as an alternative to oral pantoprazole in patients unable to continue taking pantoprazole tablets. It is not indicated for maintenance therapy for GERD.

[2]Approved for three-drug regimen with amoxicillin and clarithromycin. For patients who fail therapy, susceptibility testing should be conducted. If resistance to clarithromycin is demonstrated or susceptibility testing is not available, an alternative antimicrobial therapy should be used.

[3]Approved as part of a three-drug regimen with amoxicillin and clarithromycin; also approved as dual therapy with amoxicillin in patients who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected.

[4]Approved as part of three-drug regimen with amoxicillin and clarithromycin; also approved as part of dual regimen with clarithromycin (however, more likely to develop clarithromycin resistance with two-drug regimen). For patients who fail therapy, susceptibility testing should be conducted. If resistance to clarithromycin is demonstrated or susceptibility testing is not available, an alternative antimicrobial therapy should be used.

IV. Pharmacokinetics of the Proton Pump Inhibitors[29-36]

Though the bioavailability of the PPIs differs somewhat, all achieve peak plasma levels within a few hours after administration. All PPIs have short half-lives and are extensively protein bound. With the exception of lansoprazole, the PPIs are largely excreted in the urine as inactive metabolites; the excretion of lansoprazole is largely fecal. All PPIs are extensively metabolized in the liver.

Table 3. Pharmacokinetic Parameters of the PPIs

Proton Pump Inhibitor	Tmax* (hrs)	Half-life (hrs)	Bioavailability	Protein Binding	Metabolism	Excretion
Esomeprazole magnesium	1.6	1.5	90%	97%	CYP2C19 CYP3A4	80% urine 20% feces
Lansoprazole	1.7	1.5	80%	97%	CYP2C19 CYP3A4	33% urine 67% feces
Omeprazole	0.5 – 3.5	0.5 – 1	30-40%	95%	CYP2C19 CYP3A4	77% urine 23% feces
Pantoprazole sodium	2.5	1	77%	98%	CYP2C19 CYP3A4 Non-CYP**	71% urine 18% feces
Rabeprazole sodium	2 – 5	1 – 2	52%	96.3%	CYP3A CYP2C19	90% urine 10% feces

*Tmax = the time to peak plasma levels after oral administration

**Pantoprazole has also been reported to be metabolized by a sulphotransferase outside the CYP system.[35,36]

There are significant polymorphisms for one of the cytochrome P450 isoenzymes involved in proton pump inhibitor metabolism (CYP2C19), and this polymorphism has been shown to substantially increase plasma levels of omeprazole, lansoprazole, and pantoprazole, but not those of rabeprazole.[37] The CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15-20% of Asians lack CYP2C19 and are termed poor metabolizers.[29] At steady state, the ratio of AUC in poor metabolizers to AUC in the rest of the population (extensive metabolizers) is approximately 2.

Esomeprazole is a mixture of the S isomer of omeprazole, which is a mixture of the S and R isomers. Following administration of equimolar doses, the S and R isomers are metabolized differently in the liver, resulting in higher plasma levels of the S than the R isomer.[29] Extensive 24-hour intragastric pH monitoring studies have compared omeprazole 20mg and esomeprazole 20 and 40mg.[30] The studies revealed esomeprazole 20mg and 40mg to have superior outcomes on three measures of antisecretory effect: 1) consistency amongst individuals, 2) duration over the 24 hour cycle, 3) overall impact on pH. However, superiority in pharmacokinetic parameters must also correlate to clinical superiority in outcomes. Kinetics alone is not justification for clinical superiority.

V. Drug Interactions of the Proton Pump Inhibitor Agents[29-35, 37-39]

Table 4. Documented Drug Interactions with the PPIs

Proton Pump Inhibitor	Interacting Drugs	Mechanism
All	Ketoconazole, itraconazole	Decreased absorption of antifungals due to increased gastric pH.
All	Digoxin	Increased absorption/serum levels of digoxin due to increased gastric pH.
All	Iron salts	Decreased absorption of iron salts due to increased gastric pH.
All	Enteric-coated salicylates	Increased gastric pH may cause more rapid dissolution of enteric coating, leading to quicker release of salicylate and potentially increased gastric side effects.
All	Indinavir sulfate	Decreased gastric absorption leading to decreased antiviral activity.
All	Warfarin	Reports of increased INR and PT with several PPIs; monitor.
Omeprazole, rabeprazole	Cyclosporine	Inhibition of cyclosporine metabolism leading to potentially increased cyclosporine serum concentrations.
Lansoprazole	Theophylline	Minor increase in the clearance of theophylline; not likely to be clinically significant in most patients.
Lansoprazole, omeprazole	Sucralfate	Reduced bioavailability of PPIs; take PPI 30 minutes prior to sucralfate.
Omeprazole	Benzodiazepines*	Inhibition of oxidative metabolism leading to increased serum levels of benzodiazepines.
Omeprazole	Cilostazol	Inhibition of CYP2C19 metabolism leading to increased cilostazol serum levels.
Esomeprazole, rabeprazole, omeprazole	Clarithromycin	Increased serum levels of the PPI as well as metabolite of clarithromycin (14-hydroxyclarithromycin) may be beneficial in treatment of *H. pylori* infection.
Omeprazole	Phenytoin	Inhibition of oxidative metabolism of phenytoin leading to increased phenytoin serum levels.
Omeprazole, pantoprazole	Methotrexate	Possibly decreased renal elimination of methotrexate leading to the potential for increased adverse events.

*Excludes benzodiazepines not undergoing oxidative metabolism (e.g. lorazepam, oxazepam, temazepam).

VI. Adverse Drug Events with the Proton Pump Inhibitors[29-35,40]

In general, the proton pump inhibitors are well tolerated. The adverse events from controlled clinical trials reported in the agents' package labeling are similar in scope. The most frequently reported side effects are headache, diarrhea, nausea and abdominal pain. Table 5 below lists the reported incidence of adverse events with an incidence of one percent or more, and occurring the same or more frequently as the comparator drug(s) or placebo in controlled trials.

Table 5. Adverse Events Reported at ≥1% in Controlled Clinical Trials[29-35]

Adverse Event	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole	Rabeprazole
Headache	3.8 - 5.5%	*	2.9%	5%	2.4%
Diarrhea	4.3%	3.8%	3.7%		
Nausea		1.3%	4.0%	2%	
Flatulence			2.7%		
Abdominal pain	3.8%	2.1%	5.2%	3%	
Constipation		1%	1.5%		
Vomiting			3.2%	2%	
LFTs abnormal				2%	
Asthenia			1.3%		
Acid regurgitation			1.9%		

*Reported, but specific incidence not given.

All proton pump inhibitors are classified as pregnancy category B with the exception of omeprazole, which is classified as pregnancy category C due to sporadic reports of congenital abnormalities occurring in infants of women who received omeprazole during pregnancy.

PPIs are often used for chronic conditions. Safety concerns regarding the long-term use of PPIs were raised during the years following introduction of PPIs to the market. These concerns revolved around the effects of chronic, profound acid suppression leading to potential problems with bacterial overgrowth and nutrient absorption, as well as the development of atrophic gastritis and potentially cancer. However, long-term use of these agents has not resulted in these problems and the PPIs are generally considered safe for long-term use.[39]

VII. Dosing and Administration of the Proton Pump Inhibitors[29-35]

Table 6. Dosing and Administration of the PPIs

Indication	Esomeprazole	Lansoprazole	Omeprazole	Pantoprazole*	Rabeprazole
Gastroesophageal Reflux Disease (GERD)					
Healing of erosive esophagitis	20-40mg once daily x 4-8 weeks[1]	30mg once daily x 8 weeks[4]	20mg once daily x 4-8 weeks	40mg once daily x 8 weeks[4]	20mg once daily x 4-8 weeks[4]
Maintenance of healing of erosive esophagitis	20mg once daily[2]	15mg once daily	20mg once daily	40mg once daily	20mg once daily
Treatment of symptomatic GERD	20mg once daily x 4 weeks[3]	15mg once daily x 8 weeks	20mg once daily x 4 weeks	--	20mg once daily x 4 weeks[3]
Peptic Ulcer Disease					
Helicobacter pylori eradication to reduce the risk of duodenal ulcer recurrence	*See table below*	*See table below*	*See table below*	--	*See table below*
Healing of duodenal ulcers	--	15mg once daily x 4 weeks	20mg once daily x 4 weeks[3]	--	20mg once daily x 4 weeks
Maintenance of healed duodenal ulcers	--	15mg once daily	--	--	--
Treatment of active, benign gastric ulcer	--	30mg once daily x 8 weeks	40mg once daily x 4-8 weeks	--	--
NSAID-associated gastric ulcer: Healing Risk reduction	--	 30mg once daily x 8 weeks 15mg once daily x 12 weeks	--	--	--
Other					
Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome	--	60mg once daily to 90mg twice daily	60mg once daily to 120mg three times daily	40mg twice daily to 120mg twice daily	60mg once daily to 60mg twice daily

*Patients receiving IV pantoprazole for treatment of erosive esophagitis or hypersecretory conditions should be switched over to the oral delayed-release pantoprazole tablets as soon as possible.
[1]An additional 4-8 weeks treatment may be considered for patients not healing within this time frame.
[2]Controlled studies did not go beyond 6 months.
[3]An additional 4 weeks of treatment may be considered for patients still symptomatic after initial treatment.
[4]An additional 8 weeks of treatment may be considered for patients not healing within this time frame.

Table 7 below includes regimens for the eradication of *H. pylori* approved by the FDA, as well as drug regimens endorsed by the American College of Gastroenterology (ACG).

Table 7. Dosage Regimens for Eradication of *H. pylori*

	ACG Recommended Regimens[24]	FDA Approved Indication
PPI + BMT	**B**SS 2 tabs QID x 14d **M**etronidazole 500mg TID x 14d **T**etracycline 500mg QID x 14d + omeprazole 20mg QD x 14d or + lansoprazole 30mg QD x 14d	No
PPI + AC	**A**moxicillin 1gram BID x 10-14d **C**larithromycin 500mg BID x 10-14d PPI BID x 10-14d +pantoprazole 40mg or +omeprazole 20mg‡ or +rabeprazole 20mg or +esomeprazole 20mg or +lansoprazole 30mg	Yes*
PPI + MC	**M**etronidazole 500mg BID x 14d **C**larithromycin 500mg BID x 14d PPI BID x 14 d +pantoprazole 40mg or +omeprazole 20mg or +rabeprazole 20mg or +esomeprazole 20mg or +lansoprazole 30mg	No
Other Regimens Approved by the FDA		
XI. PPI + AC	Amoxicillin 1gram BID x 10 days Clarithromycin 500mg BID x 10 days Esomeprazole 40mg QD x 10 days	Yes
	Amoxicillin 1gram BID x 7 days Clarithromycin 500mg BID x 7 days Rabeprazole 20mg BID x 7 days	Yes
Dual Therapy‡‡	Clarithromycin 500mg TID x 14 days Omeprazole 40mg TID x 14 days**	Yes
	Amoxicillin 1gram TID x 14 days Lansoprazole 30mg TID x 14 days	Yes

‡10 day regimen approved by FDA. Continue omeprazole 20mg QD for an additional 18 days for active ulcer disease.
‡‡ No longer recommended due to lower eradication rates and antimicrobial resistance.
*Omeprazole and lansoprazole approved. The following twice daily doses of PPIs are considered equivalent: omeprazole 20mg, lansoprazole 30mg, 40mg pantoprazole, 20mg rabeprazole, 20mg esomeprazole.
**Continue omeprazole 20mg QD for an additional 14 days for patients with an active ulcer.

In general, no dosage adjustments are necessary for the geriatric population, or in patients with renal insufficiency or mild to moderate hepatic insufficiency. However, the PPIs should only be used with caution in patients with severe hepatic insufficiency, and dosage adjustments may be required. The delayed-release tablets and pellets should not be crushed or chewed.

Special Dosing Considerations

Esomeprazole

- The safety and efficacy of esomeprazole has not been established in pediatric patients. The pharmacokinetics of esomeprazole has not been studied in patients < 18 years of age.
- Esomeprazole delayed release-capsules may be opened and mixed with one tablespoon of applesauce. The mixture should be swallowed, not chewed, immediately. The mixture cannot be stored for future use and the applesauce used cannot be hot. The esomeprazole pellets have also been shown in vitro to remain intact when exposed to tap water, orange juice, and yogurt.

- Dosage adjustment is not necessary in patients with mild to moderate hepatic impairment, patients with renal impairment, or geriatric patients.
- Pregnancy category B.

Lansoprazole

- Dosage adjustment in patients with renal impairment does not appear necessary. Prevpac should not be recommended in patients with a creatinine clearance value less than 30mL/min. In patients with severe hepatic dysfunction, dosage reduction should be considered.
- The safety and effectiveness of lansoprazole in children age 1 to 11 has been evaluated for the short-term treatment of symptomatic GERD and erosive esophagitis. Safety and effectiveness has not been established in patients less than 1 year.
- Lansoprazole delayed-release capsules can be opened and administered. The contents of a capsule can be mixed with one tablespoon of applesauce, Ensure pudding, cottage cheese, yogurt, or strained pears. Capsules may also be emptied into a small volume of apple juice, orange juice, or tomato juice. In either case, the mixture should be swallowed immediately.
- The contents of a capsule can also be mixed with 40ml of apple juice and injected through a nasogastric tube (≥8 French) into the stomach. The tube should be flushed with additional apple juice.
- Lansoprazole orally disintegrating tablets are not designed to be swallowed intact or chewed. The tablet should dissolve on the tongue. The orally disintegrating tablets can be administered per nasogastric tube (≥8 French) when placed in a syringe and dissolved in water.
- Lansoprazole delayed-release oral suspension should not be given through enteral administration tubes. This can result in clogging of the tube.
- Pregnancy category B.

Omeprazole

- Dosage adjustment does not appear necessary in patients with renal impairment. Dosage adjustments should be considered in patients with hepatic impairment, especially those on long-term omeprazole therapy.
- Omeprazole delayed-release capsules may be opened and added to a tablespoon of applesauce. The mixture should be swallowed immediately and not chewed. The mixture should not be stored for future use.
- The efficacy of omeprazole has been studied in children age 2 years to 16 years for the treatment of acid-related gastrointestinal diseases, including symptomatic GERD, erosive esophagitis, and the maintenance of healing of erosive esophagitis.
- Pregnancy category C.

Pantoprazole

- Dosage adjustment is not necessary in patients with renal impairment, patients undergoing hemodialysis, patients with hepatic impairment, or in geriatric patients.
- Pantoprazole tablets should be swallowed intact and not split, crushed, or chewed. Two 20mg tablets can be used for a 40mg dose if a patient is unable to swallow the 40mg tablet.
- The safety and efficacy of pantoprazole in children younger than 18 years of age has not been established. Pharmacokinetics of pantoprazole have not been investigated in patients less than 18 years of age.
- Pregnancy category B.

Rabeprazole

- Due to a lack of clinical data of rabeprazole in patients with severe hepatic impairment, caution should be exercised in dosing this population. Accumulation of rabeprazole at the usual dose of 20mg daily is unlikely, and dose adjustments is not necessary in mild to moderate hepatic impairment. Dose adjustments are also not necessary in geriatric patients or in patients with renal impairment.
- Rabeprazole delayed-release tablets should not be chewed, crushed, or split. They must be swallowed whole.
- The safety and efficacy of rabeprazole in children younger than 18 years of age has not been established. Pharmacokinetics of rabeprazole have not been investigated in patients less than 18 years of age.
- Pregnancy category B.

VIII. Effectiveness of the Proton Pump Inhibitors

The PPIs have shown similar efficacy in the treatment of acid-related disorders, and choice of agent within this class will largely depend on formulation needed.[41-42]

GERD

A meta-analysis was conducted by Caro, Salas and Ward to compile evidence relating to the efficacy of newer proton pump inhibitors compared to omeprazole, ranitidine and placebo.[43] The objective of the study was to examine healing and relapse rates (RR) in acute and maintenance treatment of GERD in head-to-head clinical trials. Comparison of symptom control was a secondary objective. 26 studies of acute therapy and 15 studies of maintenance therapy were included in this meta-analysis. Of those included, eight trials compared acute therapy of newer PPIs versus omeprazole and 3 trials compared maintenance therapy of newer PPIs versus omeprazole. (Esomeprazole was not available on the market at the time of this study, so no comparisons included this drug.) Four of the trials comparing newer PPIs versus omeprazole evaluated symptom control. A summary of the key findings are included in Table 8 below.

Table 8. Meta-Analysis of Healing, Relapse Rates & Symptoms of GERD: Newer PPIs vs. Omeprazole[43]

Acute Therapy	**4 Weeks**	**8 Weeks**
PPI	**Healing Rates (%)**	**Healing Rates (%)**
Lansoprazole	66-86	75-93
Omeprazole	61-81	76-94
Pantoprazole	66-68	80
Rabeprazole	71-81	76-92
PPI Comparison	**RRs Compared to Omeprazole (95% CI)**	**RRs Compared to Omeprazole (95% CI)**
Lansoprazole 30mg/d vs. Omeprazole 20mg/d	1.04 (0.99-1.10)	1.02 (0.98-1.06)
Pantoprazole 40mg/d vs. Omeprazole 20mg/d	0.96 (0.85-1.08)	0.98 (0.90-1.07)
Rabeprazole 20mg/d vs. Omeprazole 20mg/d	0.92 (0.85-1.00)	0.93 (0.87-1.00)
Maintenance Therapy*		
PPI	**Relapse Rates During Initial 6 Months of Therapy**	
Lansoprazole 30mg/d	6-29%	
Omeprazole 20mg/d	7-42%	
Pantoprazole	No data	
Rabeprazole 20mg/d	9%	
GERD Symptoms		
PPI Comparison	**Resolution of GERD Symptoms at 4 Weeks: RR (95%CI)**	
	Heartburn	**Regurgitation**
Rabeprazole 20mg/d vs. Omeprazole 20mg/d	1.10 (07-1.71)	Not Reported
Pantoprazole 40mg/d vs. Omeprazole 20mg/d	1.06 (0.90-1.25) 0.95 (0.88-1.05)	1.06 (0.90-1.25) 0.92 (0.83-1.04)
Lansoprazole 30mg/d vs. Omeprazole 40mg/d	1.04 (0.90-1.21)	0.92 (0.69-1.21)

*Overall RR not reported due to limited data.

Several studies have compared esomeprazole to other PPIs and found higher healing rates of erosive esophagitis[44-45] or remission rates of healed esophagitis[46] with esomeprazole. However, there are questions as to the doses compared in these and other trials and their general applicability (e.g., two trials compared esomeprazole 40mg to omeprazole 20mg, and one study compared esomeprazole 20mg to lansoprazole 15mg). Another five-way cross-over study[47] compared gastric acid control in a small group of patients and found esomeprazole to be significantly more effective at maintaining a pH>4 as

compared to the four other PPIs. However, once again, whether the doses used were equipotent is questionable (esomeprazole 40mg, omeprazole 20mg, lansoprazole 30mg, pantoprazole 40mg, and rabeprazole 20mg). Another study found pantoprazole 40mg daily and esomeprazole 40mg daily to be equivalent in overall GERD symptom relief, while pantoprazole achieved relief of symptoms more quickly than esomeprazole.[48] The improved efficacy rates seen with some esomeprazole studies may be due more to the dose used than to improved pharmacodynamic effects.

PUD

A recent meta-analysis of triple-therapy regimens for the eradication of *H. pylori* determined that eradication rates were similar for regimens including lansoprazole, omeprazole or pantoprazole as the PPI component.[49] A randomized, double-blind study was conducted to compare eradication rates of triple therapy regimens containing omeprazole versus rabeprazole in 345 patients. Eradication rates of *H. pylori* were not statistically different between the regimens containing the different PPIs (87% per protocol with rabeprazole, 85% per protocol with omeprazole).[50] Another meta-analysis compared several different PPI-based triple therapy regimens for *H. pylori* eradication and found them to be similarly efficacious (omeprazole vs. lansoprazole, omeprazole vs. rabeprazole, omeprazole vs. esomeprazole, and lansoprazole vs. rabeprazole).[51]

Large, head-to-head studies comparing PPIs in the prevention and treatment of NSAID-induced ulcers are lacking. The OMNIUM[52] and ASTRONAUT[53] trials demonstrate the efficacy of omeprazole in facilitating ulcer healing in NSAID-users, while a third study showed the improved efficacy of lansoprazole for NSAID-induced ulcer healing as compared to an H2 receptor antagonist.[54] A recent study compared the incidence of recurrent ulcer bleeding in patients with arthritis who received either the selective COX-2 inhibitor, celecoxib, or combination therapy with diclofenac and omeprazole 20mg daily.[55] The probability of recurrent bleeding after 6 months was not significantly different between the two treatment regimens (4.9% with celecoxib and 6.4% with diclofenac + omeprazole). A trial comparing lansoprazole to placebo and misoprostol for NSAID-induced gastric ulcer prevention demonstrated that lansoprazole was superior to placebo, but not to misoprostol.[56] However, the adverse effects of misoprostol and the potential for drug noncompliance and discontinuation must be considered when comparing these two approaches.

Additional Evidence

Dose Simplification: Not Applicable.

Stable Therapy: Limited data is available on the effects of switching patients from one proton pump inhibitor to another. One documented result of switching from omeprazole to lansoprazole exists in the literature, as described by Nelson, et al. The change resulted in worsening of symptoms and decreased patient satisfaction in previously stabilized patients with heartburn or GERD.[57, 58] Results were measured by telephone survey, a subjective means of data collection.

Impact on Physician Visits: A retrospective study evaluating the impact of OTC availability of H-2 antagonists on medication prescribing patterns and utilization of physician services showed that the mean absolute number of prescriptions dispensed for H-2 antagonists was reduced by 1.5 prescriptions ($p<0.001$) and the mean number of prescriptions dispensed for all GI agents was reduced by 1.3 prescriptions ($p<0.001$).[59] OTC availability was not associated with an increase in physician visits, overall, or for GERD-related conditions.

IX. Conclusions

Studies have shown the proton pump inhibitors to be clinically similar in efficacy (healing, relapse rates, and symptoms of GERD) and side effects for acid-related disorders. Lansoprazole has the most indications, followed by omeprazole (Rx). Pantoprazole lacks an indication for *H. pylori* infections. Generic formulations are available for omeprazole 10 and 20mg capsules, and the OTC formulation is available for short-term management of heartburn.

As a result of available clinical data, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in that class and offer no significant clinical advantage over other alternatives in general use.

X. Recommendations

No brand proton pump inhibitor is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of the Topical Antibacterials
AHFS 840404
August 11, 2004

I. Overview

The topical antibacterials in AHFS class 840404 include products for the treatment or prevention of various superficial skin infections. Drugs in this class include: bacitracin, clindamycin, gentamicin, metronidazole, mupirocin, and neomycin. Many of these topical agents have been a part of treatment regimens for years. Infections of the skin and soft tissues are among the most common infections seen in both community and hospital settings.[1] Infections may involve any or all layers of the skin, fascia, and muscle. They can also spread far from the initial site of infection and lead to more severe complications. When this occurs, treatment beyond the topical agents in this class is often required. Topical antibacterials indicated for the treatment of acne and/or rosacea are considered cosmetic treatments are not included in the review.

Humans are natural hosts for many bacterial species that colonize the skin as normal flora. *Staphylococcus aureus* and *Streptococcus pyogenes* are infrequent resident flora, but they account for a wide variety of bacterial pyodermas. Factors predisposing individuals to infection include minor trauma, preexisting skin disease, poor hygiene, a high concentration of bacteria ($>10^5$microorganisms), excessive moisture of the skin, inadequate blood supply, and, rarely, impaired host immunity.[1, 2] Exposed areas of the body such as the face and neck generally have the highest bacterial density and *Staphylococcus epidermidis* is the most common organism, whereas moister areas such as the axilla and groin are most frequently colonized with gram-negative bacilli. Table 1 illustrates the predominant microorganisms of normal skin.

Table 1. Predominant Microorganisms of Normal Skin

Bacteria
Gram Positives *Staphylococcus epidermidis* *Staphylococcus aureus*
Diphtheroids *Corynebacterium* spp. *Propionibacterium* spp. *Streptococcus* spp. *Peptostreptococcus* spp. *Bacillus* spp. *Micrococcus* spp.
Gram Negatives *Enterobacteriaceae*
Yeast
Pityrosporum ovale *Candida*

Common bacterial infections of the skin are classified as primary or secondary. Primary infections usually involve previously healthy skin and are typically caused by a single pathogen. Secondary infections occur in areas of previously damaged skin and are frequently polymicrobic.

Some of the topical antibacterial agents are available as generics. They are noted in Table 2 with an asterisk (*). In addition, a few agents are available over-the-counter (OTC). This review encompasses all dosage forms and strengths.

Table 2. Topical Antibacterial Products in this Review[5, 6, 7]

Rx/OTC	Generic Name	Formulation	Example Brand Names (s)
OTC	Bacitracin*	Ointment 500u/gm	Baciguent
OTC	Bacitracin, neomycin sulfate, polymyxin B sulfate*	Ointment	HM Triple antibiotic, Neoporacin, Neosporin, Triple antibiotic, others
Rx	Bacitracin, hydrocortisone, neomycin, polymyxin B sulfate	Ointment 0.5%	Cortisporin
Rx	Hydrocortisone, neomycin, polymyxin B sulfate	Cream 0.5%	Cortisporin
OTC	Bacitracin, polymyxin B sulfate*	Ointment	Double Antibiotic, Polysporin, others
OTC	Bacitracin zinc*	Ointment 500u/gm	Bacitracin zinc
Rx	Clindamycin phosphate	Vaginal suppositories 100mg Vaginal cream 2%	Cleocin Vaginal Ovules Cleocin
Rx	Gentamicin*	Cream 0.1% Ointment 0.1%	G-myticin, Garamycin
Rx	Metronidazole	Vaginal gel 0.75%	MetroGel Vaginal
OTC	Neomycin sulfate / polymyxin B sulfate*	Cream	Antibiotic cream (various generics)
Rx	Neomycin sulfate / hydrocortisone	Ointment* 0.5%/1%	HC/neomycin sulfate
Rx	Mupirocin*	Ointment 2%	Bactroban, Centany
Rx	Mupirocin calcium	Cream 2% Ointment 2%	Bactroban Bactroban nasal

*Generic Available

II. Evidence Based Medicine and Current Treatment Guidelines

Skin Infections

Proper diagnosis, histology, and microbiology are important in the treatment of skin infections. This information typically drives the need for a particular topical antibacterial agent. The American Academy of Dermatology and the American Academy of Family Physicians issue practice guidelines for skin infections, most for more severe infections and for infections with resistant organisms.[3] Emergence of drug resistance mutant strains of microorganisms and development of irritant and allergic contact dermatitis is a common problems with many of the topical antibacterials.[4] The more complicated infections are beyond the scope of treatment with this therapy class, as they typically require systemic treatment with oral and sometimes intravenous antibiotics.

Bacterial skin infections are the 28th most common diagnosis in hospitalized patients.[3] The common skin infections include impetigo, folliculitis, furunculosis, carbunculosis, ecthyma, erysipelas, cellulites, necrotizing fasciitis, and fungal and yeast infections. The fungal infections will be addressed in a separate review of the antifungal agents. Table 2 lists the bacterial classification of select skin and soft tissue infections.

Table 3. Bacterial Classification of Important Skin and Soft Tissue Infections[1]

Primary Infections	Microorganisms
Erysipelas	Group A *streptococci*
Impetigo	*Staphylococcus aureus*, group A *streptococci*
Lymphangitis	Group A *streptococci*, occasionally *S. aureus*
Cellulitis	Group A *streptococci*, *S. aureus*
Necrotizing Faciitis Type 1 Type 2	 Anaerobes (*Bacteroides* spp., *Peptostreptococcus* spp.) and faculatative bacteria (*streptococci*, *Enterobacteriaceae*) Group A *streptococci*
Secondary Infections	
Diabetic Foot Infections	*S. aureus*, *streptococci*, *Enterobacteriaceae*, *Bacteroides* spp., *Peptostreptococcus* spp., *Pseudomonas aeruginosa*
Pressure Sores	*S. aureus*, *streptococci*, *Enterobacteriaceae*, *Bacteroides* spp., *Peptostreptococcus* spp., *Pseudomonas aeruginosa*
Bite Wounds Animal Human	 *Pasteurella multocida*, *S. aureus*, *streptococci*, *Bacteroides* spp. *Eikenella corrodens*, *S. aureus*, *streptococci*, *Corynebacterium* spp., *Bacteroides* spp., *Peptostreptococcus* spp.
Burn Wounds	*Pseudomonas aeruginosa*, *Enterobacteriaceae*, *S. aureus*, *streptococci*

Bacterial Vaginosis

Bacterial vaginosis (BV) is a disease that is characterized by vaginal discharge.[5] It is one of the most common infections of the lower genital tract in women who are of reproductive age. There are approximately three million cases in the U.S. each year.[5] BV is associated with complications including preterm birth, postpartum endometritis, post-hysterectomy infections, intrauterine infection, and increased susceptibility to HIV transmission.[8] In this condition the normal vaginal flora is replaced with an overgrowth of anaerobic microorganisms (including *Mobiluncus* spp and *Prevotella* spp) and *Gardnerella vaginalis* and *Mycoplasm hominis*.[5]

Because of the complications associated with bacterial vaginosis, all symptomatic women (particularly pregnant women) should be treated. The treatment options include oral or vaginal preparations of metronidazole and clindamycin, except in pregnant women who should not receive clindamycin vaginal gel secondary to an association with premature deliveries. Intravaginal treatment may be preferable over oral treatment due to decreased systemic effects.[8] About 80-90% of women will have an initial response to treatment.[5]

III. Comparative Indications of the Topical Antibacterials

Although minor skin infections and wounds usually heal without treatment, some minor skin wounds do not heal without therapy and it is impossible to determine at the time of injury which wounds will be self-healing. Some experts believe that, by reducing the number of superficial bacteria, topical anti-infectives are useful for *preventing* infection in minor skin injuries.[6] However, the role of most topical anti-infectives for the *treatment* of superficial skin infections has not been fully elucidated, and systemic anti-infective therapy is usually required for the treatment of serious or extensive skin infections.

Neomycin is available in combination with topical corticosteroids. Results of well-controlled clinical studies suggest that these combination products may be more effective for the treatment of infected dermatoses than either neomycin or the corticosteroid alone.[6] However, benefits of combination therapy must be weighed against reduced resistance to bacterial, fungal, or viral infections and suppression by the corticosteroid of signs and symptoms of infection or hypersensitivity.

Table 4. FDA-Approved Indications for the Topical Antibacterials[5, 6, 7]

Agent	Prevention or treatment of superficial infections alone or in combination with other anti-infectives	Treatment of superficial skin infections caused by susceptible bacteria	Bacterial Vaginosis	Impetigo	Eliminate Nasal *S. aureus***
Bacitracin	✓				
Bacitracin, neomycin sulfate, polymyxin B sulfate	✓				
Bacitracin, hydrocortisone, neomycin, polymyxin B sulfate	✓				
Hydrocortisone, neomycin, polymyxin B sulfate	✓				
Bacitracin, polymyxin B sulfate	✓				
Bacitracin zinc	✓				
Clindamycin phosphate†			✓		
Gentamicin		✓			
Metronidazole			✓		
Neomycin sulfate / polymyxin B sulfate	✓				
Neomycin sulfate / hydrocortisone	✓				
Mupirocin				✓ (Ointment only)	
Mupirocin calcium		✓* (Cream only)		✓ (Ointment only)	✓ (Age 12 and older)

*Both primary and secondary infections
**Including methicillin-resistant S. aureus (MRSA)
†Clindamycin cream can be used to treat pregnant women during the second and third trimester only.

IV. Pharmacokinetic Parameters

The available pharmacokinetic data for the drugs used in the topical antibacterial products is limited and the parameters that are available vary from drug to drug. For the most part, minimal drug is absorbed from application of the topical antibacterial agents. Table 5 details the pharmacokinetic data that is available for each drug.

Table 5. Pharmacokinetic Parameters of the Topical Antibacterial Agents[6, 7]

Agent	Systemic Absorption?	Bioavailability (%)	T_{max} (hr)	Elimination Half-Life	Protein Binding (%)
Bacitracin	No	-	-	-	-
Neomycin sulfate	No-with intact skin, Yes-through denuded areas of wounds or ulcerated skin	-	-	-	-
Polymyxin B Sulfate	The drug does not appear to be absorbed to an appreciable extent from mucous membranes.	-	-	-	-
Clindamycin phosphate	Yes-following vaginal (5%)	Intravaginal cream-5%, suppositories-30%	-	Intravaginal cream-1.5-2.6 hr, suppositories-11 hr	
Gentamicin Note: Greater absorption of drug with cream than ointment.	No-with intact skin, Yes-through denuded areas of wounds or ulcerated skin	-	-	-	-
Metronidazole	Yes-vaginal	50-56%	6-12 hours	-	<20
Mupirocin	Little	-	-	17-36 minutes	95-97
Mupirocin calcium	Minimal	-	-	17-36 minutes	95-97

V. Drug Interactions of the Topical Antibacterials

Most of the topical antibacterials in this class are not absorbed, therefore, there is little concern for drug interactions when these agents are used. However, caution with intravaginal clindamycin and metronidazole, and mupirocin, should be used in the following situations. The likelihood of systemic interactions following topical or intravaginal administration of these drugs would be less than with oral or parenteral administration.[6]

Clindamycin
Clindamycin has been shown to have neuromuscular blocking properties that may enhance the **neuromuscular blocking** action of other **agents** (e.g. ether, tubocurarine, pancuronium).[6, 9] Intravaginal clindamycin should be used with caution in patients receiving these agents and patients should be observed for prolongation of neuromuscular blockage.

Metronidazole
Systemic metronidazole potentiates the effects of **oral anticoagulants** resulting in prolongation of the prothrombin time.[6, 7, 9] Although only small amounts of drug are absorbed from topical application, the possibility that anticoagulant effects may be potentiated should be considered when the topical agents are given to patients on orally administered anticoagulants.

Disulfiram-like reactions have occurred in some patients who ingested **alcohol** while receiving oral or IV metronidazole. A disulfiram-like reaction has occurred in at least one patient who ingested alcohol while receiving intravaginal metronidazole.[6, 9] Patients should be cautioned about using alcohol during therapy with metronidazole vaginal gel.

Administration of **disulfiram** and oral metronidazole has been associated with acute psychoses in some patients, therefore, the drugs should not be used concomitantly. At least 2 weeks should elapse following the discontinuance of disulfiram prior to initiating therapy with metronidazole vaginal gel.

Short-term metronidazole therapy in patients stabilized on relatively high doses of **lithium** have been reported to increase serum lithium concentrations and cause signs of lithium toxicity in several patients.[6, 9]

Concomitant use of metronidazole and oral or IV **cimetidine** may prolong the plasma half-life and decrease the plasma clearance of metronidazole.[6]

Mupirocin
Although the clinical importance has not been determined, *in vitro* studies using *E. coli* indicate that chloramphenicol interferes with the antibacterial action of mupirocin on RNA synthesis.[6]

VI. Adverse Drug Events of the Topical Antibacterials

Some information on adverse events with the topical antibacterials is limited, however, for a few agents, there is more extensive data available. The most commonly reported adverse events with the topical antibacterials are allergic contact dermatitis and hypersensitivity type reactions. Additionally reported events are detailed below and in Table 6.[7]

Bacitracin
Rash, hypersensitivity reaction (rare).

Antibiotic combinations
Bacitracin ointment: Allergic contact dermatitis has occurred.
Neomycin: Hypersensitivity; ototoxicity and nephrotoxicity have occurred. (most likely with systemic use)

Gentamicin Sulfate
Irritation (erythema, pruritus); possible photosensitization.

Mupirocin[5, 7]
Topical ointment: Burning, stinging, or pain (1.5%); itching (1%); rash, nausea, erythema, dry skin, tenderness, swelling, contact dermatitis, and increased exudates (<1%); systemic reactions (rare).
Topical cream: Headache (1.7%); rash, nausea (1.1%); abdominal pain, burning at application site, cellulites, dermatitis, dizziness, pruritus, secondary wound infection, and ulcerative stomatitis (<1%).
Nasal: Headache (9%); rhinitis (6%); respiratory disorder including upper respiratory tract congestion (5%); pharyngitis (4%); taste perversion (3%); burning/stinging, cough (2%); pruritus (1%); blepharitis, diarrhea, dry mouth, ear pain, epistaxis, nausea, rash (<1%).

Metronidazole
In a randomized, single-blind clinical trial of 505 nonpregnant women who received metronidazole vaginal gel once or twice daily, 2 patients (1 from each regimen) discontinued therapy early because of drug-related adverse events. Medical events judged to be related, probably related, or possibly related to administration of metronidazole vaginal gel once or twice/day were reported for 39% (195/505) of patients.[7]
CNS: Headache (5%); dizziness (2%); depression, fatigue (<1%).
Dermatologic: Generalized itching or rash (<1%).
GI: GI discomfort (7%); nausea and/or vomiting (4%); unusual taste (2%); decreased appetite, diarrhea/loose stools (1%); and abdominal bloating/gas, dry mouth, thirst (<1%).
GU: Vaginal discharge (12%); symptomatic *Candida* cervicitis/vaginitis (10%); vulva/vaginal irritative symptoms (9%); pelvic discomfort (3%); darkened urine (<1%).

Clindamycin

Table 6. Adverse Events Occurring in ≥ 1% of Nonpregnant Patients Receiving Clindamycin Vaginal Cream[7]

Adverse Reaction	3 Day Cream n=600	7 Day Cream n=1325
GU		
Trichomonal vaginitis	0	1.3
Vaginal moniliasis	7.7	10.4
Vulvovaginal disorder	3.2	5.3
Vulvovaginitis	6	4.4
Miscellaneous		
Moniliasis (body)	1.3	0.2

VII. Dosing and Administration of the Topical Antibacterials

Proper use of topical antibacterials includes skin cleansing and drying prior to application of the agents. Table 7 details the dosing and administration for each antibacterial agent.

Table 7. Dosing for the Antibacterials[5, 6, 7]

Agent	Availability	Dose /Frequency/Duration
Bacitracin	Ointment 500u/gm	Apply topical ointment (size equal to the surface area of the tip of a finger) to the affected area 1-3 times daily.
Bacitracin, neomycin sulfate, polymyxin B sulfate	Ointment	Apply a small amount of the antibiotic ointment on the affected area 1 to 3 times/day.
Bacitracin, hydrocortisone, neomycin, polymyxin B sulfate	Ointment 0.5%	Apply a small amount of the antibiotic ointment on the affected area 1 to 3 times/day.
Hydrocortisone, neomycin, polymyxin B sulfate	Cream 0.5%	Apply a small amount of the antibiotic cream to the affected area 1 to 3 times/day.
Bacitracin, polymyxin B sulfate	Ointment	Apply a small amount of the antibiotic ointment on the affected area 1 to 3 times/day.
Bacitracin zinc	Ointment 500u/gm	Apply topical ointment (size equal to the surface area of the tip of a finger) to the affected area 1-3 times daily.
Clindamycin phosphate	Vaginal suppositories 100mg Vaginal cream 2%	Insert one suppository intravaginally/day, preferably at bedtime, for 3 consecutive days. Insert one applicatorful intravaginally, preferably at bedtime, for 3 or 7 consecutive days in nonpregnant women and for 7 consecutive days in pregnant women.
Gentamicin	Cream 0.1% Ointment 0.1%	Apply 3 to 4 times daily to affected area. In cases of impetigo, crusts should be removed before application. Cover treated area with gauze dressing if desired.
Metronidazole	Vaginal gel 0.75%	One applicatorful intravaginally once or twice daily for 5 days. For once-a-day dosing, administer at bedtime.
Neomycin sulfate / polymyxin B sulfate	Cream	Apply a small amount of the cream to the affected area 1 to 3 times/day.
Neomycin sulfate / HC	Ointment	Apply a small amount of ointment to the affected area 1 to 3 times/day.
Mupirocin	Ointment 2%	Apply a small amount of ointment to the affected area 3 times daily. The area may be covered with gauze dressing. Reevaluate areas not showing a response in 3 to 5 days.
Mupirocin calcium	Cream 2% Ointment 2% Nasal 2%	Apply a small amount of cream to the affected area 3 times daily for 10 days. The area may be covered with gauze dressing. Reevaluate areas not showing a response in 3 to 5 days. Apply a small amount of ointment to the affected area 3 times daily. The area may be covered with gauze dressing. Reevaluate areas not showing a response in 3 to 5 days. Divide approximately one half of the ointment from the single-use tube between the nostrils and apply twice daily for 5 days.

Special Dosing Considerations

- Clindamycin and metronidazole vaginal products are considered pregnancy category B.
- The mupirocin products are also considered pregnancy category B.
- Pediatric use of mupirocin cream has been studied and is indicated for patients age ≥3 months. To date, there have been 93 studies in this population. The ointment has been studied in patients 2 months to 16 years and the safety of the nasal formulation in children under the age of 12 years has not been established.

VIII. Comparative Effectiveness of the Topical Antibacterials

The combination antibacterial agents (neomycin/ polymyxin B/ bacitracin) have been available for treatment for many years, and there are no recent comparative studies available for these agents. However, there is comparative efficacy data, although limited, for several of the other agents in this class. Table 8 describes recent comparative studies with some of the drugs in this class.

Table 8. Additional Outcomes Evidence for the Topical Antibacterials

Study	Sample	Duration	Results
Mupirocin cream vs. oral cephalexin[5]	n=93	10 day randomized study	In evaluating the efficacy of mupirocin TID versus cephalexin 250mg QID (or 25mg/kg/day of oral suspension) for secondarily infected skin lesions: • Clinical efficacy at 7-10 days follow-up, as defined per the protocol, was 97.7% (43/44) for mupirocin cream and 93.9% (46/49) for cephalexin.
Mupirocin ointment vs. oral erythromycin[5]	n=57	8 days	In evaluating the efficacy of mupirocin ointment TID versus oral erythromycin at 30-40mg/kg per day for the treatment of impetigo: • One week following treatment, clinical efficacy rates were 93% for mupirocin ointment and 78.5% for erythromycin. • Pathogen eradication rates in the were 100% for both test groups.
Triple antibiotic ointment vs. mupirocin[10]	n=99	Randomized, prospective, interventional study	Patients presenting to the ER were either given triple antibiotic ointment or mupirocin with standard wound care. All patients were required to make a follow-up visit to determine the status of their wound (infected or not-infected). • Patients in the mupirocin group had greater rate of signs of infection (12% vs. 6.1%), and infection (4% vs. 0%) compared with patients in the triple antibiotic ointment group. There was no statistical difference between groups. • There was a similar rate of wound infection and adverse events between the triple antibiotic ointment and mupirocin ointment.
Treatment and prophylaxis of *S. aureus* colonization with mupirocin[11]	-	6 randomized, controlled trials were included in this evidence-based review	The published literature was critically appraised regarding the efficacy of intranasal mupirocin for eradication of *S. aureus* nasal carriage and for prophylaxis of infection: • Mupirocin was generally highly effective for eradication of nasal carriage in the short-term. • Prophylactic treatment of patients with intranasal mupirocin in large trials did not lead to significant reduction in the overall rate of infections. • Subgroup analysis and several small studies have revealed lower rates of *S. aureus* infection among selected populations of patients with nasal carriage treated with mupirocin.
Meta-analysis of treatments for impetigo[12]	-	Meta-analysis of 16 randomized, controlled trials	A systematic review and meta-analysis of the treatment of impetigo was conducted: • Topical antibiotics are more effective than placebo. • There is weak evidence for the superiority of topical antibiotics over some oral antibiotics, such as erythromycin. • There is no significant difference between the effects of mupirocin and fusidic acid.

Additional Evidence

Dose Simplification: Not Applicable.

Stable Therapy: Not Applicable. Medications in this review are used in acute care situations.

Impact on Physician Visits: No peer reviewed data was found in a literature search of Medline/Pubmed or Ovid. Some drugs in this class are available over-the-counter, without a physician visit to obtain a prescription.

IX. Conclusions

Use of the combination topical antibacterials (neomycin/ polymyxin B/ bacitracin) is driven by self-medication with the over-the-counter agents. Many of these agents are also available as generics.

There are comparative studies with mupirocin, however, they are primarily with oral antibiotics. Use of mupirocin nasal has not been found to be beneficial and is not indicated for the prevention of autoinfection of high risk patients from their own nasal colonization. There is also not sufficient data to use mupirocin nasal for general prophylaxis of any infection in any patient population. Larger, head-to-head studies are needed to access any superiority of mupirocin over the other topical antibacterial agents.

Additionally, metronidazole and clindamycin vaginal agents for the treatment of bacterial vaginosis are not available generically, but are the topical treatments of choice for this condition and may be preferable over oral treatment due to decreased systemic effects. Treating bacterial vaginosis is important and can result in decreases in preterm births, postpartum endometritis, post-hysterectomy infections, and intrauterine infections.

Therefore, clindamycin and metronidazole vaginal agents offer significant clinical advantage in general use over the generics and OTC products but are comparable to all other brands in this class. However, the remaining agents in the topical antibacterial class are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternative in general use.

X. Recommendations

Alabama Medicaid should work with the manufacturers of the brands of clindamycin vaginal and metronidazole vaginal on cost proposals so that at least one brand is selected as a preferred agent. In addition, there is no brand recommended for preferred status of the remaining antibacterial agents in this class.

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Pharmacotherapy Review of the Topical Antivirals
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I. Overview

Both acyclovir and penciclovir are synthetic nucleoside analogs derived from guanine. These agents are active against various Herpesviridae including herpes simplex virus types 1 and 2 (HSV-1 and HSV-2).[1]

The two most common cutaneous manifestations of the herpes simplex virus infection are orolabial and genital herpes. Herpes genitalis is one of the most common viral sexually transmitted diseases in the world, with an estimated seroprevalence in the United States of greater then 20%.[2] About 5% of women of childbearing age have clinically evident genital herpes, with 25-30% having subclinical infections.[3] The causative agent in most cases of genital herpes (85%) is herpes simplex virus-2 (HSV-2), while the incidence of herpes simplex virus-1 (HSV-1) is growing. Most persons infected with HSV-2 have not been diagnosed. Many such persons have mild or unrecognized infections but shed virus intermittently in the genital tract. After resolution of primary infection, the virus persists in the nerve roots of the sacral plexus, often causing recurrent (often less severe) outbreaks.

Orolabial herpes is the most prevalent form of mucocutaneous herpes infection, with 35-60% of white persons in the United States showing serologic evidence of having been infected by HSV-1.[4] Overall, the highest rate of infection occurs during the preschool years.

Before the 1970's, when acyclovir (Zovirax) was introduced as an antiviral drug, cutaneous HSV infection was managed with drying agents and other local care. Today, treatment options include multiple oral antiviral agents and topical antiviral agents. Oral treatments are effective in reducing symptoms, while intravenous administration may be required in immunocompromised patients and those with severe disseminated infection.[4] Topical acyclovir reduces the duration of viral shedding and the length of time before all lesions become crusted, but this treatment is much less effective than oral or intravenous acyclovir.

This review compares the two topical antiviral agents. The topical antiviral products are available as an ointment (acyclovir only) or cream (acyclovir and penciclovir) formulation. There are no generic alternatives available for the topical antiviral agents. This review encompasses all of the dosage forms (topical) and strengths.

Table 1. Products In This Review

Generic Name*	Formulation	Example Brand Name
Acyclovir	Ointment 5% (50mg/g)	Zovirax
	Cream 5% (50mg/g)	
Penciclovir	Cream 1% (10mg/g)	Denavir

*There are no generic formulations available for any of the medications in this class.

II. Treatment Guidelines

Topical antiviral therapies in the treatment of HSV infections are substantially less effective than systemic therapy. However, initial application of topical antivirals on lesions during the prodromal syndrome has been documented to decrease the duration of viral sheding.[1] The International Herpes Alliance and the Centers for Disease Control (CDC) and Prevention have made recommendations for the treatment of genital herpes. Tables 1 and 2 summarize the recommendations.

Table 2. Treatment Guidelines for Genital Herpes

International Herpes Alliance[5]
• Begin oral antiviral treatment for patients with suspected first episode genital herpes without waiting for laboratory test results to confirm a diagnosis. • Confirmation of the infection is essential, however, as first episodes may be severe and starting treatment before test results are available may help to avoid the development of complications. • It can be some time from initial infection until herpes virus can be detected. Blood tests to detect viral infection may not be of use in the early stages of infection because antibodies may take up to 8-12 weeks to develop. Even if a test returns negative, the possibility of infection may not be ruled out. • Patients seeing their physician within 5 days of the start of the episode, or while they are developing new sores, should be given oral antiviral drugs because they are more effective than topical preparations.

Table 3. 2002 CDC Sexually Transmitted Diseases-Genital Herpes Simplex Virus Infecitons[6]

Centers for Disease Control and Prevention Guidelines[6]
• Systemic antiviral drugs partially control the symptoms and signs of herpes episodes when used to treat first clinical episodes and recurrent episodes or when used as daily suppressive therapy. • Topical therapy with antiviral drugs offers minimal clinical benefit, and its use is not recommended. • **Initial episode**: One of the following regimens. Acyclovir 400mg TID for 7-10 days Acyclovir 200mg five times daily for 7-10 days Famciclovir 250mg orally TID for 7-10 days Valacyclovir 1gm BID for 7-10 days Treatment can be extended if healing is incomplete after 10 days. • **Recurrent episodes of HSV disease**: One of the following regimens. Acyclovir 400mg TID for 5 days Acyclovir 200mg fives times daily for 5 days Acyclovir 800mg BID for 5 days Famciclovir 125mg BID for 5 days Valacyclovir 500mg BID for 3-5 days Valacyclovir 1gm QD for 5 days • **Suppressive therapy for recurrent genital herpes**: One of the following regimens. Note: Safety and efficacy of daily therapy with acyclovir has been established for 6 years, and with valacyclovir or famciclovir for 1 year. Acyclovir 400mg BID Famciclovir 250mg BID Valacyclovir 500mg QD Valacyclovir 1gm QD • **Severe disease**: IV acyclovir therapy should be provided for patients who have severe disease or complications that necessitate hospitalization. The recommended regimen is acyclovir 5-10mg/kg body weight IV Q8 hours for 2-7 days or until clinical improvement is seen. • Counseling: Counseling of infected patients and their sex partners is critical to management of genital herpes. Counseling should help patients cope with the infection and prevent sexual and perinatal transmission. • Cancer risk: The misconception that HSV causes cancer should be dispelled, because the role of HSV-2 in cervical cancer is at most that of a cofactor, not a primary etiologic agent.

III. Indications of the Topical Antivirals

Although topical therapy with acyclovir may be used for the management of initial genital herpes, topical therapy is not usually recommended for the treatment of genital herpes. Topical use of acyclovir does not appear to be effective in the treatment or prevention of infections caused by latent herpes viruses in neuronal ganglia. Acyclovir ointment should not be used for prevention of recurrent HSV infections.[1]

Table 4. Topical Antiviral Indications[7, 8]

Generic Name	FDA Approved Indications
Acyclovir	Management of initial episodes of herpes genitalis and in limited non-life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients.
	Treatment of recurrent herpes labialis (cold sores) in adults and adolescents.
Penciclovir	For the treatment of recurrent herpes labialis (cold sores) in adults.

IV. Pharmacokinetic Parameters

Table 5. Pharmacokinetic Parameters of the Topical Antiviral Agents[1, 9]

Agent	Documented Kinetic Parameters
Acyclovir	**Absorption** **Ointment:** Systemic absorption after topical application is minimal. One study showed no drug detected in blood or urine after use, while another study detected drug in the blood of 9 of 11 patients and urine of all patients. Plasma levels ranged from less than 0.01 to 0.28mcg/mL and in urine less than 0.02% to 9.4% of the daily dose was excreted. **Cream:** Plasma concentration was measured in 6 adults who received the cream applied 5 times a day, every 2 hours for 4 days. Daily urinary excretion of acyclovir averaged 0.04% of the daily dose applied, and plasma acyclovir concentrations were below the limit of detection in 5 of the subjects and barely detectible in 1 patient. Systemic absorption was minimal. **Distribution, Elimination** Distribution of acyclovir following topical administration has not been determined. *In vitro* acyclovir appears to be distributed in cells that are infected with the herpes virus. The metabolic fate of percutaneously absorbed acyclovir has not been fully determined. What little drug is absorbed topically is eliminated via the kidneys.
Penciclovir	Measurable penciclovir concentrations were not detected in plasma or urine of healthy volunteers following single or repeat application of the 1% cream at a dose of 180mg daily.

V. Drug Interactions

Due to limited systemic absorption of both acyclovir and penciclovir, no drug interactions are likely to occur and none are documented with the topical antiviral agents.[10]

VI. Adverse Drug Events

Adverse events with the topical antiviral agents are rare. Since little drug is absorbed, most adverse events that do occur are local.

Table 6. Documented Common Adverse Drug Events with the Topical Antivirals[7, 8]

Agent	Adverse Events
Acyclovir ointment	• Mild pain with transient burning/stinging (30%) • Pruritus (4%) • Edema/pain at application site • Rash
Acyclovir cream	• Dry/cracked lips, pruritus, stinging (less than 1%) • Angioedema, contact dermatitis, eczema
Penciclovir cream	• Application site reactions • Taste perversion • Rash

VII. Administration and Dosing

Table 7. Dosing and Administration of the Topical Antiviral Agents[7, 8, 9]

Agent	Formulation	Dose and Administration
Acyclovir	Ointment 5% (50mg/g)	**For Herpes Genitalis:** Apply sufficient quantity to adequately cover all lesions every 3 hours, 6 times daily for 7 days. (Therapy should be initiated as early as possible following onset of signs and symptoms).
	Cream 5% (50mg/g)	**For Herpes Labialis:** Apply 5 times daily for 4 days.
Penciclovir	Cream 1% (10mg/g)	**For Herpes Labialis:** Apply every 2 hours during waking hours for a period of 4 days. Treatment should be started as early as possible (e.g. during the prodrome or when lesions appear).

Special Dosing Considerations

- Acyclovir topical is a pregnancy category B drug.
- Penciclovir is a pregnancy category B drug.
- Acyclovir cream can be used for the treatment of cold sores in adolescents 12 years of age and older. The safety and efficacy of acyclovir ointment has not been established in pediatric patients.
- The safety and efficacy of penciclovir in pediatric patients has not been established.

VIII. Effectiveness

Acyclovir

In clinical trials of initial genital herpes infections, acyclovir appeared to reduce healing time and in certain instances, decrease duration of viral shedding and pain. In studies with immunocompromised patients mainly with herpes labialis, there was a decrease in duration of viral shedding and a slight decrease in duration of pain.[7]

In studies involving recurrent genital herpes and herpes labialis in nonimmunocompromised patients, there did not appear to be any evidence of clinical benefit. However, some decrease in duration of viral shedding was recorded.[7]

Penciclovir

In two double-blind, placebo controlled trials in patients with recurrent herpes labialis, penciclovir was shown to shorten the mean duration of lesions by one-half day shorter than the placebo groups. Treatment was initiated within 1 hour of noticing signs of symptoms and continued for four days.[8]

Table 8. Additional Clinical Efficacy Studies for the Topical Antiviral Agents

Study	Sample	Duration	Results
Penciclovir vs. acyclovir for genital herpes[11] Note: penciclovir is not indicated for the treatment of genital herpes	n=205	7 day randomized, double-blind, multicenter trial	To explore the efficacy of topical treatment of genital herpes with penciclovir 1% cream, patients were enrolled who had a clinical diagnosis of genital herpes: • There was encouraging improvement in both treatment groups although no significant differences in clinical efficacy with respect to clinical cure rate, times to healing, resolution of symptoms, absence of blisters, cessation of new blisters, crusting, and loss of crust between penciclovir and acyclovir. • A significantly shorter time to crusting was found in the penciclovir group as compared to the acyclovir group. • Adverse reactions were reported infrequently.
Penciclovir vs. acyclovir for herpes labialis[12]	n=40	4 days	In comparing topical penciclovir with acyclovir in patients with an excess of five recurrences annually: • Results confirmed, with regards to time to lesion crusting and resolution of pain, that penciclovir is superior to acyclovir.
Penciclovir for herpes labialis[13]	n=3,057	Two 5 day randomized, double-blind, parallel group trials in North America and Europe	In evaluating the efficacy and safety of topical 1% penciclovir cream to that of placebo in a immunocompetent population: • Penciclovir treated patients lost classical lesions 31% faster than did placebo patients (P=0.0001), and experienced 28% faster resolution of lesion pain (P=0.0001). • Significant benefits were achieved with penciclovir use whether treatment was initiated in the early stages (P=0.001) of later stages (P=0.0055).
Penciclovir vs. placebo for herpes labialis[14]	n=2209	4 day randomized, multicenter, double-blind, placebo-controlled trial	In comparing the safety and efficacy of topical penciclovir cream with placebo for the treatment of recurrent episodes of herpes simplex labialis in immunocompetent patients: • Healing of classical lesions (vesicles, ulcers, and/or crusts) was 0.7 day faster for penciclovir-treated patients compared with those who received vehicle control cream (median, 4.8 days vs. 5.5 days; P<.001). • Pain (median, 3.5 days vs. 4.1 days; P<.001) and lesion virus shedding (median, 3 days vs. 3 days; P=.003) also resolved more quickly for penciclovir-treated patients compared with patients who applied the vehicle control. • The efficacy of penciclovir cream was apparent when therapy was initiated early (prodrome or erythema lesion stage) and when initiated late (papule or vesicle stage).
Acyclovir vs. placebo for herpes labialis[15]	n=699	Two 4 day treatment, randomized, double-blind, vehicle-controlled,	Healthy volunteers with a history of frequent herpes labialis were given acyclovir 5% cream or a vehicle control: • In study 1, the mean duration of episodes was 4.3 days for patients treated with acyclovir cream and 4.8 days for those treated with the vehicle control (P = 0.007).

		multicenter trials	• In study 2, the mean duration of episodes was 4.6 days for patients treated with acyclovir cream and 5.2 days for those treated with the vehicle control (P = 0.006). • Efficacy was apparent whether therapy was initiated "early" (prodrome or erythema lesion stage) or "late" (papule or vesicle stage). • There was a statistically significant reduction in the duration of lesion pain in both studies. • Acyclovir cream did not prevent the development of classical lesions (progression to vesicles, ulcers, and/or crusts).

Additional Evidence

Dose Simplification: Not Applicable.

Stable Therapy: Not Applicable. Medications in this review are used in acute care situations.

Impact on Physician Visits: One study in patients with suspected genital herpes isolated the herpes simplex virus in 2,088 of 3,602 patients, with 90.2% of isolates being HSV-2.[16] Fifteen isolates, all HSV-2, were acyclovir resistant. Of HIV negative patients, 0.18% of patients had acyclovir resistant isolates, compared to HIV positive patients where 5.3% of patients yielded resistant HSV isolates. Resistance was observed with both oral and topical acyclovir use, although resistance to the drug in immunocompetent patients remains low. Resistance patterns may influence physician visits due to treatment failure. No additional peer reviewed data was found in a literature search of Medline/Pubmed and Ovid pertaining to topical antivirals and physician visits. A discussion on the treatment of genital herpes and medical utilization is included in the keratolytics review.

IX. Conclusions

Although acyclovir ointment is indicated for use in the treatment of initial episodes of genital herpes in immunocompromised patients, it is not usually recommended for use in the treatment of genital herpes in general use. According to the CDC, use of topical antivirals offers little clinical benefit and should not be recommended. For the treatment of herpes labialis, penciclovir cream has shown slight clinical benefit over acyclovir in the time to crusting of herpes lesions in two small comparative studies. However, clinical cure rates, times to healing, and resolution of symptoms do not appear to be different for treatment with penciclovir or acyclovir.

Therefore, all brand products within the topical antiviral class are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

X. Recommendations

No brand topical antiviral is recommended for preferred status.

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I. Overview

Superficial mycoses are among the most common infections in the world and fungal infections are the second most common vaginal infection in North America.[1] Fungal infections have been reported as far back as 1839, and over the past 15-20 years, occurrence rates of some fungal infections have increased dramatically. One reason for an increase in fungal infections is likely the treatment of patients with HIV and those whose immune system are compromised. The prevalence of fungal skin infections varies throughout parts of the world, from the most common causes of skin infections in the tropics to relatively rare disorders in the United States.

The topical antifungal agents are used for dermatological conditions from athlete's foot (tinea pedis), to ringworm, oral candidiasis, and other dermatophytoses infections (tinea infections). Vulvovaginal candidiasis, 80-92% caused by *C. albicans,* appears to be increasing, possibly related to use of over-the-counter vaginal antifungal preparations, short-course therapy, and/or the increased use of long-term maintenance therapy in preventing recurrent infections.[1] Table 1 lists the common tinea infections.

Table 1. Common Tinea Infections[1, 2]

Tinea Infection	Affected Body Area
Tinea capitis	Head
Tinea barbae	Beard
Tinea corporis	General skin
Tinea cruris	Groin
Tinea manuum	Hands
Tinea pedis	Feet
Tinea unguium	Toenails

This review encompasses all dosage forms and strengths. Table 2 lists the antifungal products included in this review.

Table 2. Products in this Review[3, 4, 5]

Antifungal Classification	Generic Name	Formulation	Example Brand Name (s)	Rx/OTC
Allylamines	Naftifine	1% Cream, Gel	Naftin	Rx
	Terbinafine	1% Cream, Solution	Lamisil AT, Lamisil Lamisil, Lamisil AT Spray Pump	OTC OTC
Azoles	Butoconazole nitrate	2% Cream	Gynazole-1	Rx
	Clotrimazole			
	Oral:	10mg Lozenges	Mycelex	Rx
	Topical:	1% Cream*	Lotrimin, Lotrimin AF, Lotrimin AF Jock Itch Cream, Cruex, Desenex, Lotrimin, Lotrimin AF, Anti-fungal cream, Clotrim, Mycelex, various generics	OTC/Rx‡
		1% Lotion	Fungoid, Lotrimin, Lotrimin AF	OTC
		1% Solution*	Gyne-Lotrimin, Mycelex-7	OTC/Rx‡
	Vaginal:	1% Cream* 7-day	Gyne-Lotrimin –3, Clotrim, Fungoid, various generics	OTC
		2% Cream* 3-day	Gyne-Lotrimin 3, Clotrimazole 3 Day, Femcare, various generics	OTC
		Kit	Gyne-Lotrimin-3	OTC
		100mg Tablet*		100mg OTC
		500mg Tablet*		500mg Rx
		200mg Suppositories*	Gyne-Lotrimin-3	OTC
	Clotrimazole 1% / betamethasone dipropionate 0.05%	Lotion Cream*	Lotrisone Lotrisone	Rx
	Econazole nitrate	1% Cream*	Spectazole	Rx
	Ketoconazole	2% Cream*	Nizoral	Rx
		2% Shampoo*		Rx
		1% Shampoo	Nizoral A-D	OTC
	Miconazole nitrate			
	Topical:	1%, 2% Aerosol*	Ting, Desenex, Lotrimin AF Athlete's Foot, Micatin Athlete's Foot Desenex Jock Itch Spray Powder, Lotrimin AF, Micatin, Ting	OTC
		2% Aerosol Powder*	Micatin, Microguard, Podactin	OTC
		1% Cream*	Antifungal Cream, various generics	OTC
		2% Cream*	Zeasorb-AF, Baza Antifungal, Carrington Antifungal, Micaderm, Micatin, Microguard, Mitrazol, Secura Antifungal, Podactin, Triple Care, various generics	OTC
		2% Lotion	Desenex, Lotrimin AF, Zeasorb AF	OTC
		2% Powder*	Micatin, Lotrimin AF, Zeasorb-AF, Breezee Mist	OTC
		2% Tincture	Fungoid	OTC
	Vaginal:	2% Cream*	Monistat 7, Monistat 3, Gyne-Stat 7, various generics	OTC
		100mg Supp.*	Monistat 7	Rx/OTC‡
		200mg Supp.*	Monistat 3	Rx/OTC‡
		Kit*	Monistat 3, Monistat 1 Combo	Rx/OTC‡

	Miconazole nitrate / hydrocortisone	Cream	Fungoid & HC	Rx
	Oxiconazole nitrate	1% Cream 1% Lotion	Oxistat	Rx
	Sulconazole nitrate	1% Cream 1% Solution	Exelderm	Rx
	Terconazole	Vaginal Cream 0.4%, 0.8%* Vaginal Supp. 80mg	Terazol 3*, Terazol 7 Terazol 3	Rx Rx
Azoles	Tioconazole-1	6.5% Vaginal Oint.*	Monistat-1, Vagistat-1	OTC
Benzylamines	Butenafine HCl 1%	Cream	Mentax Lotrimin Ultra	Rx OTC
Misc. Antifungals	Benzoic acid 6%/ Salicylic acid 3%	Ointment	Bensal HP	Rx
	Clioquinol 3% Clioquinol 3%w hydrocortisone 1%	Cream* Ointment, Cream*	Clioquinol Hydrocortisone with Clioquinol	OTC Rx
	Salicylic acid / sodium thiosulfate	Lotion*	Versiclear	Rx
Polyenes	Nystatin Topical: Vaginal:	Cream100,000u/g* Ointment100,000u/g* Powder100,000u/g* Tablets100,000u/g *	Mycostatin, Nystex Mycostatin, Nystex Mycostatin, Nystop, Pedi-Dri Mycostatin	Rx Rx Rx Rx
	Nystatin 100,000u/g / 0.1% triamcinolone	Cream* Ointment*	Mycogen II, Mycolog II, Myconel, Myco-Triacet II, Mytrex, N.T.A. Mycogen II, Mycolog II, Myco-Triacet II, Mytrex, N.T.A.	Rx
Thiocarbamates	Tolnaftate	1% Aerosol* 1% Aerosol Pwdr.* 1% Cream* 1% Powder* 1% Solution*	Aftate, Tinactin, Ting Aftate, Breezee, Tinactin Tinactin, Ting Tinactin Tinactin	OTC OTC OTC OTC OTC
Hydroxypyridones	Ciclopirox Ciclopirox Olamine	0.77% Gel, Shampoo 8% Solution 0.77% and 1% cream, lotion	Loprox Penlac Loprox	Rx Rx Rx

*Generic Available

‡ Products are available OTC or Rx, depending on product labeling.

II. Current Treatment Guidelines

Commonly, the tinea infections are named for the body part affected. Tinea infections are superficial fungal infections caused by three genera of dermatophytes: Trichophyton, Microsporum and Epidermophyton.[2] For the most part, dermatomycosis is typically confined to the superficial keratinized tissue and can be treated with topical antifungal medications.

Most tinea corporis, cruris, and pedis infections can be treated with topical agents. Consideration should be given to systemic treatment when lesions covering a large body-surface area fail to clear with repeated treatment using different topical agents. Environmental factors should also be addressed, in the event any such factors may exacerbate the infection. The following recommendations from the American Academy of Family Physicians and the American Academy of Dermatology Association highlight treatment of antifungal infections.

Table 3. Treatment of Common Superficial Tinea Infections[2]

The American Academy of Family Physicians
Nonpharmacologic Measures • Patients should be encouraged to wear loose-fitting garments made of cotton or synthetic materials designed to wick moisture away from the surface of the skin. • Areas likely to become infected should be dried completely before being covered with clothes. • Patients should also be encouraged to avoid walking barefoot and sharing garments.
Pharmacologic Treatments The antifungal agents can be grouped by structure and mechanism of action. The two principal treatment groups are the azoles and the allylamines. The polyenes (amphotericin B and nystatin) are not effective in the treatment of most dermatophyte infections. • Tinea corporis and tinea cruris require once to twice daily treatment for 2 weeks. • Tinea pedis may require treatment for 4 weeks. • All treatments should continue for at least 1 week after symptoms have resolved. • Some newer agents require only once daily application and shorter courses of treatment, and are associated with lower relapse rates. • Application of the topical agent should include normal skin about 2cm beyond the affected area. • Combination therapy (antifungal plus steroid) should be considered when inflammation is present. • Powders and sprays may be used to prevent reinfection. • Lotions should be used in intertriginous or hairy areas and on oozing lesions. • Creams should be used on non-oozing and moderately scaling lesions. • Ointments are preferred for hyperkeratotic lesions. • Ciclopirox (Penlac) is approved for the treatment of onychomycosis, but has limited efficacy.

Table 4. Guidelines of Care for Superficial Mycotic Infections of the Skin: Onychomycosis[3]

The American Academy of Dermatology Association
Diagnostic Tests • Greater diagnostic accuracy occurs if the clinical diagnosis is verified by laboratory tests, especially for cases where systemic treatment may be necessary. Such tests can be performed in a physician's office at the time of the patient visit and yields immediate results. Such tests include: Potassium hydroxide preparation (KOH), fungal culture, nail clippings for histologic analysis, and nail biopsy only to establish the diagnosis when other tests are negative. **Treatment** • It should be explained to the patient that topical therapy alone may not be successful in eradicating distal subungual onychomycosis (the most common type of onychomycosis). • Systemic therapy should rarely be given unless diagnosis of onychomycosis has been confirmed by a KOH preparation, fungal culture, or nail biopsy. • Treatment of fingernails with systemic agents may require as long a 6 months and systemic treatment for toenails as long as 12-18 months, and more than one course of treatment may be necessary due to reinfection. • Systemic therapy with griseofulvin and ketoconazole are indicated when a dermatophyte is isolated. • Topical therapy when *Candida albicans* is isolated may be used as an adjuvant therapy to oral fluconazole, ketoconazole or itraconazole. • For superficial white onychomycosis (an infection of the superficial nail plate surface), topical antifungals combined with surgical curettage or scraping of the infected portions of the nail plate may be effective.

III. Comparative Indications

There are numerous agents in this class available for topical and vaginal antifungal infections. Some products are available over-the-counter. Table 5 details Food and Drug Administration (FDA) approved indications for each drug.

Table 5. FDA-Approved Indications for the Topical Antifungals[4, 5, 6]

Agent	Dermatophytoses (tinea infections)	Cutaneous Candidiasis	Superficial Mycoses	Vulvovaginal Candidiasis	Seborrheic Dermatitis and Dandruff	Onycho-mycosis	Candidal Diaper Dermatitis
Naftifine	✓	✓					
Terbinafine	✓*						
Butoconazole				✓†			
Clotrimazole Oral: Topical: Vaginal:	✓*	✓[1] ✓	✓	✓†			
Clotrimazole / betamethasone dipropionate	✓*	✓	✓				
Econazole nitrate	✓*	✓					
Ketoconazole Cream: Shampoo:	✓*	✓			✓		
Miconazole nitrate Topical: Vaginal:	✓*	✓	✓	✓†			
Miconazole nitrate / hydrocortisone	✓*	✓	✓				
Oxiconazole nitrate	✓*	✓					
Sulconazole nitrate	✓*						
Terconazole				✓†			
Tioconazole	✓	✓	✓	✓†			
Butenafine HCl	✓*						
Benzoic acid / salicylic acid	✓‡						
Clioquinol	✓						
Clioquinol / hydrocortisone	✓						
Salicylic acid / sodium thiosulfate	✓*						
Nystatin Topical: Vaginal:		✓		✓			✓
Nystatin / triamcinolone		✓					
Tolnaftate	✓*						
Ciclopirox	✓*	✓			✓	✓ (Penlac)	

*Includes tinea versicolor.
†Complicated and noncomplicated.
[1] Oropharyngeal Candidiasis.
‡Benzoic acid is an astringent and salicylic acid is a keratolytic.

Pharmacology and Mechanisms of Action

Allylamines

Naftifine and terbinafine are applied once daily and remain active in the skin for up to one week after application.[2] Both agents have fungicidal activity and are structurally related. Terbinafine is more active than azole derivatives against dermatophytes, but is less active than these drugs against *Candida* spp.[4] Results of controlled trials indicate that naftifine 1% cream is equivalent in efficacy and safety to topical clotrimazole 1% cream.

Azoles

The azole agents have broad-spectrum activity, including activity against some gram-positive bacteria. Ketoconazole, sulconazole and oxiconazole require only once daily application because of their long durability in the superficial layers of the skin. Clotrimazole, miconazole, and econazole require twice daily application.

Benzylamines

Butenafine, the only benzylamine, has a structure similar to that of the allylamines. The drug is fungicidal for dermatophytes in vitro.[2] Butenafine is applied once daily and, after four weeks of use, is associated with high cure rates and a long disease-free interval.

Polyenes

Nystatin has fungistatic or fungicidal activity against a variety of pathogenic and nonpathogenic yeasts and fungi. The drug exerts its activity by binding to sterols in the fungal cell membrane. Nystatin is not active against organisms that do not contain sterols in their cell membrane.[4]

Thiocarbamates

Tolnaftate, a narrow-spectrum antifungal agent, has no antibacterial or anticandidal activity. The drug is effective when given twice daily for most dermatophytoses and for the treatment of tinea versicolor.

Hydroxypyridones

Ciclopirox is a broad-spectrum antifungal agent with activity against dermatophytes, yeasts, and some bacteria. The drug also has antibacterial activity against gram-negative and gram-positive bacteria. Ciclopirox nail lacquer has limited efficacy for use in the treatment of onychomycosis, and use of this product requires daily application for up to 48 weeks and monthly follow-up for nail debridement.

IV. Pharmacokinetic Parameters of the Topical Antifungal Agents

In general, the topical antifungal agents are not absorbed or are absorbed minimally when used for superficial fungal infections. Table 6 indicates specific data from the literature for each drug.

Table 6. Pharmacokinetic Parameters of the Antifungal Agents[4, 5]

Agent	Absorption	Distribution	Metabolism /Elimination
Naftifine	3-6% of dose is absorbed systemically	Not known	Elimination: renal and feces, half-life is 2-3 days
Terbinafine	Highly variable; some patients have no detectable plasma levels.	-	Renal elimination
Butoconazole	1.7% of vaginal dose reaches systemic circulation	Not known	Metabolism in the liver, elimination: renal and feces
Clotrimazole	Very small amounts absorbed after topical application. About 3-10% of an intravaginal dose reaches systemic circulation.	-	-
Ketoconazole	Is not appreciably absorbed after topical administration.	-	-
Miconazole	Vaginal: small amount absorbed; reports indicate the drug is not absorbed through intact skin.	-	1% of drug is recovered in urine and feces
Oxiconazole	Not appreciably absorbed after topical administration; small amounts absorbed	Distributed in horny layer of the epidermis, corium, and subcutis. Also penetrates the nail plate.	Less than 0.3% of a dose is excreted in urine within 5 days. Feces excretion is not known.
Sulconazole	12% of a dose is absorbed through the skin	Not known	Elimination: 6.7% urine and 2% feces
Terconazole	5-16% of a topical dose is absorbed	Not known	-
Tioconazole	Small amounts are absorbed systemically; Administration of a 300mg dose of 6% ointment results in a peak concentration of 18ng/ml.	Drug persists in vaginal fluid for 24-72 hours; intravaginal concentrations sufficient to inhibit fungal growth for up to 2-3 days after dose.	Is not metabolized in vaginal fluid; a portion of systemically absorbed drug is metabolized. Following intravaginal dosing, any absorbed drug is eliminated from plasma within 72 hours.
Butenafine	Following 14 days of topical treatment, the C_{max} of the drug was 1.4ng/mL and the T_{max} was 15 hours	-	Elimination: renal
Clioquinol	2-3% of dose is absorbed systemically; when used with an occlusive wrap for 12 hours, 40% of the dose was absorbed	-	-
Sodium Thiosulfate	-	-	-
Nystatin	Is not absorbed through intact skin or mucous membranes	-	-
Tolnaftate	-	-	-
Ciclopirox	Following use of nail lacquer for 6 months, systemic absorption was less than 5% of the applied dose. Percutaneous absorption of ciclopirox olamine is rapid but minimal	Drug penetrates thick horny layers of skin as well as fingernails; penetration increases with extent of mycotic infection	Elimination half-life of ciclopirox olamine is 1.7 hours; ciclopirox has an elimination half-life of 5.5 hours. Renal is the primary elimination route.

V. Drug Interactions

While systemic absorption of the antifungal agents varies, with such little absorption with most of the agents, it is unlikely usual topical application of these agents would result in systemic interactions. There are no antifungal drugs with interactions that would result in a significant clinical disadvantage of that drug over the other drugs in the class. Studies and documented case reports have defined minor interactions with some of the topical antifungal agents. The results are described below.

Clotrimazole
The use of clotrimazole troches in a liver transplant patient has been reported to increase plasma tacrolimus levels. It is suspected that clotrimazole inhibits the metabolism of tacrolimus in the gut wall, causing tacrolimus concentrations to be increased, with increased risk of toxicity. This interaction is a significance level 4 interaction (level 1 interactions are the most severe).[7]

Econazole nitrate
In vitro studies indicate that corticosteroids (e.g. hydrocortisone and triamcinolone) inhibit the antifungal activity of econazole nitrate against *Saccharomyces cerevisiae* and *Candida albicans* in a concentration-dependent manner, but have no effect on the antibacterial activity of econazole against *Staphylococcus.* When the concentration of the corticosteroid was equal to or greater than that of econazole on a weight basis, the antifungal activity was substantially inhibited, however, when the corticosteroid was only one-tenth that of econazole nitrate, the antifungal activity was unaffected.[4]

Ketoconazole
Although the clinical important has not been established, ketoconazole and acyclovir have shown dose-dependent, synergistic, antiviral activity against herpes simplex virus types 1 and 2 in in vitro replication studies. Ketoconazole and vidaradine showed interference, indifference, or antagonism in vitro against these viruses.[4]

Sulconazole
Because studies indicate sulconazole may act as a mild inducer of the cytochrome P-450 isoenzymes CYP1A1 and CYP2B1, the drug theoretically could induce the metabolism of warfarin and other drugs metabolized by these isoenzymes. However, with small amounts of sulconazole absorbed following topical administration, it is unlikely that such drug interactions would occur with topical application.[4]

Terconazole
The efficacy of intravaginal terconazole is not affected by concomitant use of oral contraceptives, nor does administration of intravaginal terconazole appear to affect estradiol or progesterone concentrations in women receiving low-dose oral contraceptives.[4]

VI. Adverse Drug Events of the Topical Antifungals

The topical antifungals are usually well tolerated. Most adverse events that do occur are local. Contact dermatitis has been reported following topical application of imidazole-derivative azole antifungals (e.g. clotrimazole, econazole, miconazole, oxiconazole, sulconazole, and tioconazole). Cross- sensitization appears to occur among the imidazole derivatives; however, cross-sensitivity appears to be unpredictable. Table 7 compares the adverse event profiles of the different antifungal agents.

Table 7. Documented Adverse Events for the Antifungals[4, 5, 6]

Adverse Event	Adverse Events
Naftifine	**Cream:** burning/stinging (6%); dryness (3%); erythema, itching, local irritation (2%). **Gel:** burning/stinging (5%); itching (1%); erythema, rash, tenderness (0.5%).
Terbinafine	In clinical trials, 0.2% of patients discontinued therapy because of adverse events and 2.3% reported adverse reactions, including irritation (1%); burning (0.8%); itching, dryness (0.2%).
Butoconazole	2% of patients report adverse events that include vulvovaginal burning, itching, soreness and swelling, and/or pelvic or abdominal pain or cramping. Headache, urinary frequency and burning, and vulvovaginal discharge, irritation, stinging, and odor occurred rarely during treatment.
Clotrimazole	**Troches:** abnormal liver function test; elevated AST levels were reported in 15% of patients in clinical trials. Other adverse events reported included nausea; vomiting; unpleasant mouth sensations; pruritus. **Topical:** erythema; stinging; blistering; peeling; edema; pruritus; urticaria; burning; general skin irritation. **Vaginal:** burning; erythema; irritation; and intercurrent cystitis.
Ketoconazole	**Cream:** severe irritation, pruritus, stinging (5%); painful allergic reaction (reported in one patient). **Shampoo:** increase in normal hair loss, irritation (< 1%); abnormal hair texture; scalp pustules; mild dryness of skin; itching; oiliness/dryness of hair and scalp.
Miconazole	**Topical:** isolated reports of irritation, burning, maceration and allergic contact dermatitis. **Vaginal:** vulvovaginal burning, itching, and irritation in a small percentage of patients. Pelvic cramps, vaginal burning, headache, hives, and skin rash have occurred rarely.
Oxiconazole	Pruritus (0.4% to 1.6%); burning (0.7% to 1.4%); stinging (0.1% to 0.7%);irritation, contact dermatitis, scaling, tingling, pain, dyshidrotic eczema (0.4%); folliculitis (0.3%); erythema (0.2%); papules, rash, nodules, maceration, fissure (0.1%).
Sulconazole	Itching, burning, stinging (3%); redness(1%).
Terconazole	Adverse events are rare and require discontinuance of drug in about 2-4% of patients. Vulvovaginal burning, pruritus, or irritation have occurred in 1-5% of patients receiving terconazole.
Tioconazole	Common adverse events: vulvovaginal burning, vaginitis, and pruritus (reported in 5-6% of women). In one small study, vulvovaginal irritation and pruritus occurred in up to 30% of patients receiving a single dose. Systemic effects: headache (5%), infection (3%), and abdominal pain (2%) have occurred after a single dose of tioconazole.
Butenafine	Burning/stinging, itching, and worsening of the condition (about 1%);contact dermatitis, erythema, irritation, and itching (less than 2%). No patient treated with butenafine discontinued treatment because of an adverse event.
Clioquinol	Local irritation, rash, and sensitivity reactions have been reported occasionally.
Sodium Thiosulfate	Irritation and sensitivity reactions.
Nystatin	Virtually nontoxic and nonsensitizing; well tolerated by all age groups including debilitated infants, even on prolonged administration. If irritation occurs, discontinue use.
Tolnaftate	A few cases of sensitization have been confirmed; mild irritation has occurred.
Ciclopirox	**Cream:** pruritus at site of application, worsening of the clinical signs and symptoms, burning. **Gel:** skin burning sensation upon application, which occurred in approximately 34% of seborrheic dermatitis patients and 7% of tinea pedis patients. Contact dermatitis and pruritus (1% to 5%); dry skin, acne, rash, alopecia, pain upon application, eye pain, and facial edema (less than 1%). **Nail Lacquer:** periungual erythema and erythema of the proximal nail fold (5%); nail disorders (e.g., shape change, irritation, ingrown toenail, discoloration), application site reactions and/or burning of the skin (1%); mild rash.

VII. Dosing and Administration

Table 8 lists specific dosing instructions for use of the topical antifungal agents.

Table 8. Dosing for the Topical Antifungal Agents[4, 5, 6]

Agent	Availability	Dose /Frequency/Duration
Naftifine	1% cream and gel	Gently massage a sufficient quantity into the affected area and surrounding skin once a day with the cream, or twice a day (morning and evening) with the gel. Wash hands after application. If no clinical improvement is seen after 4 weeks of treatment, re-evaluate the patient. Note: Occlusive dressing should not be used.
Terbinafine	1% cream of solution	**Interdigital tinea pedis** Apply to cover the affected and immediate surrounding areas twice daily until clinical signs and symptoms are significantly improved. In many patients, this occurs by day 7. Duration should be for a minimum of 1 week and should not exceed 4 weeks. ***Spray:*** Twice daily for 1 week or as directed by physician. **Tinea cruris or tinea corporis** Apply to cover the affected and immediate surrounding areas once or twice daily until clinical signs and symptoms are significantly improved. In many patients, this occurs by day 7 of therapy. Therapy should be for a minimum of 1 week and should not exceed 4 weeks. ***Spray:*** Once daily for 1 week or as directed by physician. **Tinea versicolor** Apply the 1% solution twice daily for 1 week. Therapy should be for a minimum of 1 week and should not exceed 4 weeks. **Note:** The safety and efficacy of terbinafine topical use in children younger than 12 years of age have not been established.
Butoconazole	2% cream	The recommended dose is 1 applicatorful of cream intravaginally once (Gynazole·1); or insert 1 applicatorful a day, preferably at bedtime for 3 consecutive days.
Clotrimazole	Oral 10mg lozenges Topical 1% cream 1% lotion 1% solution Vaginal 1% cream 7 day 2% cream 3 day Combination Kit 100mg, 500mg tablets 200mg suppositories	**Lozenges** Dissolve slowly one lozenge over 15-30 minutes 5 times daily for 14 consecutive days. **Suppositories** Insert 1 suppository intravaginally at bedtime for 3 consecutive days (200mg). **Intravaginal** **Cream** Insert 1 applicatorful a day, preferably at bedtime, for 3 to 7 consecutive days. **Tablets** Insert 2 100mg tablets (200mg total) intravaginally once daily for 3 days, or insert one 100mg tablet once daily for 7 consecutive days. Additionally, for uncomplicated infections, a single-dose 500mg vaginal tablet may be given. **Topical** Apply to affected areas twice daily (morning and evening) for 7 consecutive days or as needed.
Ketoconazole	2% cream, 1% and 2% shampoo	**Cream** Cutaneous candidiasis, tinea corporis, tinea cruris and tinea versicolor Apply once daily to cover the affected and immediate surrounding area. Clinical improvement may be seen fairly soon after treatment is begun; however, treat candidal infections and tinea cruris and corporis for 2 weeks in order to reduce the possibility of recurrence. Patients with tinea versicolor usually

		require 2 weeks of treatment. Patients with tinea pedis require 6 weeks of treatment. **Seborrheic dermatitis** Apply to the affected area twice daily for 4 weeks or until clinical clearing. **Shampoo** **Dandruff** Moisten hair and scalp thoroughly with water. Apply sufficient shampoo to produce enough lather to wash scalp and hair and gently massage it over the entire scalp area for 1 minute. Rinse hair thoroughly with warm water. Repeat, leaving shampoo on scalp for an additional 3 minutes. After the second thorough rinse, dry hair with towel or warm air flow. **Maintenance:** Shampoo twice a week for 4 weeks with at least 3 days between each shampooing, and then intermittently as needed to maintain control.
Miconazole	Topical 1%, 2% aerosol 2% aerosol powder 2% cream 2% lotion 2% powder 2% tincture Vaginal 2% cream 100mg, 200mg suppositories Combination Kit	**Cream** **Topical** Apply to affected areas twice daily (morning and evening) for up to 7 days or as needed. **Intravaginal** Insert 1 applicatorful intravaginally once daily at bedtime for 3 to 7 days. **Suppositories** Insert 1 suppository intravaginally once daily at bedtime for 1 day (1200mg), 3 consecutive days (200mg), or 7 consecutive days (100mg). **Aerosol and powder products** Apply sparingly to the affected area twice daily.
Oxiconazole	1% cream, lotion	Apply cream or lotion to affected area and immediately surrounding areas once or twice daily for tinea pedis, tinea corporis and tinea cruris. Apply cream only to affected areas once daily for tinea versicolor. Treat tinea corporis, tinea cruris and tinea versicolor for 2 weeks and tinea pedis for 1 month to reduce the possibility of recurrence. If a patient shows no clinical improvement after the treatment period, review the diagnosis.
Sulconazole	1% cream and solution	Gently massage a small amount into the affected and surrounding skin areas once or twice daily, except in tinea pedis, where administration should be twice daily. Early relief of symptoms is experienced by the majority of patients and clinical improvement may be seen fairly soon after treatment is begun. To reduce the possibility of recurrence, treat tinea cruris, tinea corporis and tinea versicolor for 3 weeks and tinea pedis for 4 weeks. If significant clinical improvement is not seen after 4 to 6 weeks of treatment, consider an alternate diagnosis.
Terconazole	0.4%, 0.8% vaginal cream, 80mg vaginal suppositories	**Suppositories** Administer 1 suppository intravaginally once daily at bedtime for 3 consecutive days. **Cream** 0.4% Administer one applicatorful (5g) intravaginally once daily at bedtime for 7 consecutive days. 0.8% Administer one applicatorful (5g) intravaginally once daily at bedtime for 3 consecutive days.

Tioconazole	6.5% vaginal ointment	**For use in nonpregnant adults and children 12 years of age or older:** The contents of one prefilled applicator should be inserted intravaginally high in the vaginal vault at bedtime.
Butenafine	1% cream	**Tinea versicolor, tinea corporis, or tinea cruris** Apply butenafine cream once daily for 2 weeks. **Interdigital tinea pedis** Apply butenafine twice daily for 7 days or once daily for 4 weeks.
Benzoic acid / salicylic acid	Ointment	Apply to affected area.
Clioquinol	3% cream	Apply topically 2-4 times daily for 4 weeks (Athlete's foot or ringworm) and for 2 weeks when treating jock itch.
Clioquinol / hydrocortisone	3%/1% ointment, cream	Apply topically 2-4 times daily for 4 weeks (Athlete's foot or ringworm) and for 2 weeks when treating jock itch.
Salicylic acid / sodium thiosulfate	Lotion	A thin layer should be applied topically in the form of a 25% lotion, twice daily, and continued for several weeks to months.
Nystatin	Cream, ointment, powder 100,000u/g Vaginal tablets 100,000u/g	**Cream, Ointment, Powder** Apply to affected areas 2 to 3 times daily, or as indicated, until healing is complete. For fungal infection of the feet caused by *Candida*, dust the powder freely on the feet as well as in shoes and socks. The cream is usually preferred in candidiasis involving intertriginous areas; very moist lesions, however, are best treated with powder. **Vaginal Tablets** The usual dosage is 1 tablet inserted high in the vagina by means of applicator daily for 2 weeks.
Tolnaftate	1% aerosol 1% aerosol powder 1% cream 1% powder 1% solution	Only small quantities are required. Treatment twice a day for 2 or 3 weeks is usually adequate, although 4 to 6 weeks may be required if the skin has thickened. Continue treatment to maintain remission. The choice of vehicle is important for these products. Ointments, creams and liquids are used as primary therapy. In general, powders are used as adjunctive therapy, but they may be acceptable as primary therapy in very mild conditions.
Ciclopirox	0.77% gel, shampoo 8% solution	**Loprox** Gently massage gel into the affected and surrounding skin areas twice daily, morning, and evening. Clinical improvement usually occurs within the first week of treatment. Treat interdigital tinea pedis and tinea corporis for 4 weeks. If no improvement occurs after 4 weeks of treatment, reevaluate the diagnosis. Patients with tinea versicolor usually exhibit clinical and mycological clearing after 2 weeks of treatment. **Shampoo** Wet hair and apply approximately 1 teaspoon (5mL) of the shampoo to the scalp. Up to 2 teaspoons (10mL) may be used for long hair. Lather and leave on hair and scalp for 3 minutes. A timer may be used. Avoid contact with eyes. Rinse off. Repeat treatment twice weekly for 4 weeks, with a minimum of 3 days between applications. **Penlac** Apply once daily (preferably at bedtime or 8 hours before washing) to all affected nails with the applicator brush provided. Apply evenly over the entire nail plate. If possible, apply to the nail bed, hyponychium, and the undersurface of the nail plate when it is free of the nail bed (e.g., onycholysis). Do not remove product on a daily basis. Make daily applications over the previous coat and remove with alcohol every 7 days. Repeat this cycle throughout the duration of therapy.

		Use as a component of a comprehensive management program for onychomycosis. Removal of the unattached, infected nail, as frequently as monthly, by a health care professional, weekly trimming by the patient, and daily application of the medication are all integral parts of this therapy.
Ciclopirox Olamine	0.77% and 1% cream and lotion	**Loprox** Gently massage cream, gel, or suspension into the affected and surrounding skin areas twice daily, morning, and evening. Clinical improvement usually occurs within the first week of treatment. Treat interdigital tinea pedis and tinea corporis for 4 weeks. If no improvement occurs after 4 weeks of treatment, reevaluate the diagnosis. Patients with tinea versicolor usually exhibit clinical and mycological clearing after 2 weeks of treatment.

Special Dosing Considerations

- Naftifine: Pregnancy category B. Safety and efficacy in pediatrics has not been established.
- Terbinafine: Pregnancy category B.
- Butoconazole: Pregnancy category C. Safety and efficacy in pediatrics has not been established.
- Clotrimazole: Pregnancy category B.
- Ketoconazole: Pregnancy category C. Safety and efficacy in pediatrics has not been established.
- Miconazole: Pregnancy category C.
- Nystatin: Pregnancy category C.
- Ciclopirox: Pregnancy category B. Safety and efficacy of the nail lacquer in pediatrics has not been established. Although seborrheic dermatitis can appear in puberty, no clinical studies have evaluated use of the shampoo in patients younger than 16 years.

VIII. Comparative Effectiveness of the Topical Antifungal Agents

Table 9. Outcomes Evidence for the Antifungals

Study	Sample	Duration	Results
Ciclopirox nail lacquer efficacy[6]	n=223, n=237	2 double-blind placebo studies, both lasting 48 weeks	In evaluating the efficacy of ciclopirox nail lacquer in patients with onychomycosis who had 20-65% involvement of the great nail plate: • Complete cure was achieved in 5.5% and 8.5% of patients from the 2 trials. Only one of the trials was statistically significant (the latter) compared with placebo. • Almost cure was achieved in 6.5% and 12% of patients in the study.
Terbinafine vs. clotrimazole[8]	n=217	12 week multicenter, prospective, randomized, double-blind study	In comparing terbinafine 1% cream BID for 1 week (followed by placebo cream) with clotrimazole 1% cream BID for 4 weeks in the treatment of confirmed dermatophyte infection: • After one week of treatment, 84.6% of the terbinafine patients had negative cultures compared to only 55.8% in the clotrimazole group. • Terbinafine achieved mycological cure more rapidly than clotrimazole.
Terbinafine vs. miconazole[9]	n=48	10 week double-blind, randomized trial	To compare the efficacy of terbinafine cream for 1 week with the efficacy of miconazole cream for 4 weeks in the treatment of tinea pedis, 48 patients were randomized to one treatment: • Mycological cure and clinical efficacy throughout the study were similar in both treatment groups. • After 10 weeks of follow-up, mycological cure was seen in about 52.6% and 55%, and clinical efficacy in about 47% and 45% in the terbinafine and miconazole treatment groups, respectively.

			• Treatment with terbinafine for 1 week was as good as miconazole therapy for 4 weeks.
Terbinafine vs. ketoconazole[10]	n=65	4 week prospective, comparative, randomized trial	In evaluating the safety and efficacy of 1% terbinafine gel with that of ketoconazole 2% cream in the treatment of tinea corporis and tinea cruris: • At 4 weeks, rates of mycological cure were 94% for terbinafine and 31% for patients in the ketoconazole group (P=0.002). • Four patients (1 in the terbinafine group and 3 in the ketoconazole group) had contact dermatitis-like side effects.
Naftifine cream vs. econazole cream[11]	n=104	4 week double-blind, randomized study	To evaluate the efficacy of naftifine 1% cream or econazole nitrate 1% cream patients were assigned to one treatment for BID therapy for 4 weeks. Results showed: • After 1 week of therapy, naftifine had an overall cure rate of 19% compared with 4% for econazole (P=0.03). • A difference in favor of naftifine, although not statistically significant after the first week, persisted throughout treatment. • Two weeks after the end of treatment, both medications had overall cure rates of approximately 80%. • 3% of the naftifine treated patients and 13% of the econazole treated patients had adverse events. Two patients in the econazole group had side effects severe enough to warrant discontinuation of treatment.
Naftifine vs. clotrimazole[12]	n=57	6 weeks	In evaluating the efficacy of naftifine cream 1% to clotrimazole cream 1% when applied for 4-6 weeks for tinea pedis: • More naftifine-treated patients than clotrimazole treated patients were mycological cured and globally improved, although differences were not statistically significant. • A similar trend favoring naftifine was observed in the resolution of signs and symptoms. • Treatment differences as early as 2 weeks suggest that naftifine may have a more rapid onset of action than clotrimazole.
Butoconazole 2% single dose vs. miconazole 7-day cream[13]	n=223	30 day randomized, parallel, multicenter study	In comparing the safety and efficacy of a single vaginal dose of butoconazole nitrate 2% sustained-release cream with a seven-day schedule of miconazole nitrate vaginal cream 2%, in the treatment of vulvovaginal candidiasis: • At the 30-day follow-up exam, 86% of patients given miconazole were clinically cured and 77% were culture negative, while 88% of the butoconazole patients remained clinically cured and 74% had negative fungal cultures. • On the first day of treatment, the number of patients with severe symptoms declined from 20% to 6% in the butoconazole group and from 23% to 19% in the miconazole group. • The single dose butoconazole relieved severe symptoms faster than after the first dose of miconazole (P=0.01). • All other efficacy parameters were not statistically significant.
Terconazole vs. miconazole[14]	n=900	7 days of treatment in a randomized, multicenter trial	In evaluating the efficacy of 0.4% or 0.8% terconazole cream versus 2% miconazole nitrate cream in patients diagnosed with vulvovaginal candidiasis: • After 7 days of treatment, the combined microbiologic and clinical cure rates were 87.9% for the terconazole 0.4% group, 83.8% for the 0.8% terconazole group, and 81.3% for the 2% miconazole nitrate group. • The terconazole 0.4% group consistently provided a greater degree of symptom relief and significantly fewer adverse genital-reproductive reactions as compared with 2% miconazole nitrate.

Single dose tioconazole vs. 3-day clotrimazole[15]	n=80	Single dose versus 3-day dosing	In evaluating the efficacy of a single dose of 6.5% tioconazole ointment to that of a 3-day course of 100mg clotrimazole vaginal tablets for the treatment of vulvovaginal candidiasis: • 84% of the tioconazole treated patients remained asymptomatic 4 weeks posttreatment, compared with 85% of patients treated with clotrimazole. • 59% of patients who received tioconazole and 62% who received clotrimazole remained culture negative 4 weeks after therapy. • Of the patients who received tioconazole, 30% experienced local irritation or itching, compared to 5% treated with clotrimazole ($p<0.01$).

Additional Evidence

Dose Simplification: One-dose vaginal antifungal treatments are available over-the-counter. No peer reviewed studies on adherence to topical antifungals were found in a literature search of Medline/Pubmed and Ovid.

Stable Therapy: Not Applicable. Medications in this review are used in acute care situations.

Impact on Physician Visits: Some drugs in this class are available over-the-counter, without a physician visit to obtain a prescription. An analysis evaluated the change of vaginal antifungal products from prescription to OTC status on utilization of healthcare services.[16] The analysis showed there was a decline in the number of vaginitis physician visits from 1990 to 1994 that could have been attributed to the availability of the OTC antifungal preparations. Another study looking at the effect of the Rx-to-OTC switch of vaginal antifungal agents showed the number of prescriptions dispensed for these products was reduced by 6.42 per 100 female members ages 11 and older, for the one-year period following OTC availability.[17] Physician visits for vaginitis were reduced by 0.66 per 100 members.

IX. Conclusions

Many of the differences found between the topical antifungal agents is in their differing onsets of action. The studies above confirmed the topical and vaginal agents are similarly effective. Studies do not indicate a significant clinical response with use of the ciclopirox nail lacquer. While terbinafine and clotrimazole when used topically offer similar effectiveness, terbinafine may have a more rapid cure versus clotrimazole. A similar result was seen with naftifine versus econazole and clotrimazole. Naftifine, although clinically comparable at endpoint, appears to have a more rapid onset of effectiveness. The vaginal butoconazole single-dose formulation quickly relieves symptoms and is more convenient than miconazole 7-day, however, clinical endpoints are the same with regards to effectiveness. The effectiveness of the single-dose tioconazole agent is similar to that of the 3-day clotrimazole product, in the treatment of vulvovaginal candidiasis.

With some of these agents available over-the-counter and in generic formulations, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the antifungal class and offer no significant clinical advantage over other alternatives in general use.

X. Recommendations

No brand topical antifungal is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of the Scabicides and Pediculocides
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I. Overview

Pediculosis and scabies are caused by ectoparasites. Pediculosis or lice, obligate human parasites, are either on the head (*Pediculus capitis*), body (*Pediculus humanus*), or the pubic region (*Pediculosis pubis*). Scabies, a parasitic mite, is caused by *Sarcoptes scabiei.* These skin infections, while associated with low morbidity, are common causes of skin rash and pruritus and are occurring with increasing frequency. [1,2]

Although some data suggest a growing resistance to permethrin in the United States, all reviewed resources still recommend it as first line antiparasitic therapy for treatment of both scabies and lice infections. [3] Lindane, while still widely used, is considered second line therapy due to its toxicity risks.[4]

This review includes both prescription and nonprescription topical agents for scabies and lice treatment. The drugs included in this review are detailed in Table 1. Lindane, permethrin, and piperonyl butoxide/pyrethrins products are available as generics. This review encompasses all dosage forms and strengths.

Table 1. Topical Antiparasitics (Scabicides and Pediculocides) in this Review [5-9]

Generic Name	Example Brand Name (s)	Dosage Form	Rx vs. OTC
Crotamiton	Eurax	Cream 10%, Lotion 10%	Rx
Lindane‡*	Generic only	Lotion 1%, Shampoo 1%	Rx
Malathion	Ovide	Lotion 0.5%	Rx
Permethrin*	Elimite, Acticin, Nix, various generics	Cream 5%, Lotion 1%, Liquid 1%	Rx, OTC
Piperonyl Butoxide/Pyrethrins*	Tisit, A-200, Pronto, Pyrinyl Plus, RID, Lice-Aid, Lice-X, Licide, Medi-Lice, various generics	Lotion, Gel, Shampoo, Mousse	OTC

‡Lindane is gamma benzene hexachloride. Note: brand name Kwell (lindane) is no longer available.
Rx-prescription.
OTC-over the counter, available without a prescription.
*Generic Available

II. Current Treatment Guidelines

The Centers for Disease Control and Prevention (CDC) has recommended regimens for treatment of pediculosis pubis and of scabies as part of the 2002 Sexually Transmitted Diseases Guidelines.[10] These are summarized in Table 2.

The only other recently published American guidelines are for head lice. These were published in 2002 by the American Academy of Pediatrics.[11] Table 3 includes the recommendation of permethrin as the primary treatment; included too are important points regarding school policies on treatment of head lice infestations.

Table 2. Treatment Recommendations for Pediculosis pubis and Scabies from the 2002 CDC STD Treatment Guidelines[10]

Pediculosis Pubis (Pubic Lice)
Permethrin (Nix) 1% creme rinse applied to affected areas and washed off after 10 minutes, OR Lindane 1% shampoo applied for 4 minutes to the affected area and then thoroughly washed off. This regimen is not recommended for pregnant or lactating women or for women aged < 2 years, OR Pyrethrins with piperonyl butoxide (Tisit, A-200, Pronto, etc.) applied to the affected area and washed off after 10 minutes.
Scabies
Permethrin (Elimite, Acticin) cream 5% applied to all areas of the body from the neck down and washed off after 8-14 hours. Alternative regimens: Lindane 1% lotion (1oz) or cream (30g) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after 8 hours OR Ivermectin (Stromectol) 200mcg/kg orally, repeated in 2 weeks.

Table 3. American Academy of Pediatrics 2002 Head Lice Guidelines [11]

- Pediatricians should be knowledgeable about head lice infestations and treatments and should be available as information resources for families, schools, and other community agencies.
- School personnel involved in detection of head lice infestation should be appropriately trained. The importance and difficulty of correctly diagnosing an active head lice infestation should be acknowledged. Schools should examine any lice related policies they may have with this in mind.
- **Permethrin 1% (Nix)** is currently the recommended treatment for head lice, with retreatment in 7 to 10 days if live lice are seen. Instructions on proper use of products should be carefully relayed. Safety and efficacy should be taken into account when recommending any product for treatment of head lice infestation.
- None of the currently available pediculocides are 100% ovicidal and resistance has been reported with lindane, pyrethrins, and permethrin. Treatment failure does not equate with resistance, and most instances of such failure represent misdiagnosis/ misidentification or noncompliance with the treatment regimen.
- Head lice screening programs have not been proven to have a significant effect on the incidence of head lice in the school setting over time and are not cost-effective. Parent education programs may be helpful in the management of head lice in the school setting.
- Manual removal of nits after treatment with a pediculocide is not necessary to prevent spread. In the school setting, removal may be considered to decrease diagnostic confusion.
- No healthy child should be excluded from or allowed to miss school time because of head lice. "No nit" policies for return to school should be discouraged.

III. Indications of the Scabicides and Pediculocides

The FDA approved indications for the topical antiparasitics are summarized in Table 4.

Table 4. FDA Approved Indications of Topical Scabicides and Pediculocides [5-9]

Scabies	Elimite (and generic permethrin) Eurax Lindane
Pediculosis	**Head Lice** Nix (and generic permethrin) Ovide **Head and Pubic Lice** Lindane **Head, Body, and Pubic Lice** Lice Aid and generic Piperonyl/ pyrethrins

IV. Pharmacokinetic Parameters of the Scabicides and Pediculocides

Pharmacokinetic data on the topical antiparasitics are limited. Lindane has the most available information. It had 10% systemic absorption when applied to human forearms and left for 24hrs. Peak blood levels of 63ng/mL are achieved after 6 hours of total body application. Lindane has a half-life of 18 hrs. Data suggest a rapid distribution phase followed by a longer beta elimination phase.[6] Absorption varies widely, depending on the preparation. Also, not surprisingly, those with excoriated skin absorb more lindane.[1]

Ovide has a reported 8% absorption from an acetone formulation; however, no data is available on commercially available lotion formulations in the United States.[7] For Elimite, less than 2 % is absorbed from a 5% cream. This is rapidly metabolized by ester hydrolysis to inactive metabolites that are excreted primarily in the urine.[8] For Eurax, plasma concentrations peak at 20mcg/L at 24 hours after an application. Repeat applications (this agent is also used to treat scabies-associated itching and thus may have daily use) did not show further increases in plasma concentrations.[1]

V. Drug Interactions

There are no significant drug interactions with topical antiparasitic agents.[1,5-9] Of note however, is that lindane should be used with caution with any drug that is known to lower the seizure threshold. These include antipsychotics, antidepressants, theophylline, cyclosporine, mycophenolate, tacrolimus, penicillins, imipenem, fluoroquinolones, choroquine, pyremethamine, isoniazid, meperidine, radiographic contrast media, centrally active anticholinesterases, and methocarbamol.[6]

VI. Adverse Drug Events

Overall the topical antiparasitics are well tolerated. A comparison of most commonly observed adverse effects are summarized in Table 5.

Table 5. Comparative Adverse Effects of the Scabicides and Pediculocides [5-9]

Product	Adverse Effect
Elimite, Acticin, Nix, generic permethrin	Cream - Mild transient burning/stinging, itching, tingling, numbness, erythema, or rash, headache, fever, dizziness, abdominal pain, diarrhea, nausea, vomiting, seizures. Lotion - Itching, redness, swelling of scalp.
Eurax	Allergic sensitivity, primary irritation.
Lindane	Seizure risk (see Table 6), alopecia, dermatitis, headache, pain, paresthesia, pruritus, urticaria.
Ovide*	Irritation of skin and scalp. Conjunctivitis if eye contact occurs.
Tisit, A-200, Pronto, generic piperonyl/pyrethrins	None listed.

* Ovide is an insecticide/pesticide. Inadvertent transdermal absorption of oral ingestion will manifest as excessive cholinergic activity (e.g. increased sweating, salivary and gastric secretion, GI and uterine motility, and bradycardia) Additionally, Ovide contains flammable alcohol and should not be exposed to an open flame or electric heat, including hair dryers and electric curlers.

The FDA issued a Public Health Advisory regarding lindane in March 2003. [4] A new boxed warning was added to the product labeling for all forms of lindane. Table 6 details this information.

Table 6. 2003 FDA Warnings Added to Lindane Product Labeling[6]

- Lindane should only be used in those who cannot tolerate or in those who fail first-line treatment for scabies or lice.
- Seizures and deaths have been reported with repeated application, but they have also been observed following a single application.
- Lindane products should be used with caution in infants, children, the elderly, those with other skin conditions, and in those who weigh less than 110lbs (50kg), due to risk of serious neurotoxicity.
- Lindane should not be used in premature infants and in those with known seizure disorders.
- Instruct patients on the proper amount of lindane to apply and how long to leave it on. Itching is common after scabies or lice are eradicated and is not an indication for retreatment.

VII. Dosing and Administration of the Scabicide and Pediculocide Products

In general, the shampoo products are applied for a limited amount of time and then rinsed out of hair. Cream and lotions are applied all over and not rinsed off until 8-12 hours later. For lice, products usually contain fine-toothed nit combs for removal of dead lice and eggs.[5-9]

Patients should be informed that itching occurs after the successful killing of scabies or lice and it is not necessarily an indication for retreatment. For scabies, demonstrable living mites after 14 days indicate that retreatment is necessary. [5-9]

Specific dosing and administration instructions for each product are summarized in the Appendix 1, immediately following the references for this review.

Special Dosing Considerations

- Crotamiton: It is not known whether crotamiton can cause fetal harm when administered to pregnant women or affect reproduction capacity. The safety and efficacy of crotamiton has not been established in children.
- Lindane: Pregnancy category B and is not recommended by the CDC for use in pregnancy or nursing women. Lindane is contraindicated in premature neonates due to an increase in skin permeability. The CDC currently recommends alternative treatments be used in infants and children younger than 2 years of age.

- Malathion: Safety and efficacy of malathion 0.5% lotion in children younger than 6 years of age has not been established. Topical products should not be applied to the scalp of infants and neonates and is contraindicated. Additionally, malathion lotion that is commercially available in the U.S. is flammable and everyone should be warned to stay away from lighted cigarettes, open flames, and electric heat sources while their hair is wet with the lotion.
  Malathion should be used or handled during pregnancy only when clearly needed. There have been no adequate controlled studies on pregnant women at this time.
- Permethrin: Pregnancy category B. Safety and efficacy of permethrin 1% cream rinse and 5% cream in children younger than 2 months of age have not been established. However, the drug has been used effectively without unusual adverse effect in this age group.
- Pyrethrins with piperonyl butoxide: Pregnancy category C.

VIII. Effectiveness of Scabicides and Pediculocides

Topical products remain the mainstay of therapy for the treatment of scabies and pediculosis. For scabies, in addition to topical therapy, it is important for close contacts and household members to be treated as well. Washable items like towels, sheets, and clothes should be laundered in warm to hot water; items that are not washable should not be touched for at least 3 days. [1,2]

Overall, the success rates of topical scabicides when compared to each other are 89-100% with Elimite, 65-92% with lindane, and 60 to 88% with Eurax, (Table 7). Elimite is recommended as first-line therapy and lindane as second-line in the CDC guidelines. [10] Eurax also has a role as an antipruritic for those with scabies.[5]

Oral ivermectin (Stromectol) is included in Table 7 in studies where it was compared to topical therapy. (Note: ivermectin is not being reviewed as part of this AHFS class) Two doses of Stromectol, given one week apart, appear very successful in treating scabies. The CDC recommends use of oral Stromectol as an alternative regimen for scabies, although this is not an FDA approved use at this time.[10] Stromectol may have an important role in places with endemic scabies, such as long-term-care-facilities. All patients treated for scabies should expect the rash and itching to continue for about 2 weeks after treatment.[2]

For treatment of pediculosis, as with scabies, bed linens, towels, and clothing should be washed. Sexual contact should be avoided in those with pediculosis pubis. Retreatment may be needed, particularly with head lice. Eyelashes may be treated with something occlusive such as petrolatum (Vaseline) twice daily for 10 days.[2]

Table 8 summarizes clinical efficacy studies for topical pediculosis treatments. Overall, the success rates of topical pediculocides when compared to each other are 57-99% with Nix, 60-88% with lindane, 45-95% with Tisit, A-200, etc., and 78% with Ovide. Oral Bactrim may also be useful. Combing or 'bug-busting' was only 38% successful in a comparison to malathion (78%) and should not be considered a first-line therapy for treatment of head lice. The CDC recommends Nix, lindane, or Tisit, A-200, etc. as equivalent therapies for pediculosis pubis.[10] The American Academy of Pediatrics recommends Nix for head lice.[11]

Reasons for treatment failures for either scabies or pediculosis include misdiagnosis, noncompliance, failure to follow instructions correctly, not enough pediculocide applied, reinfestation, and resistance. If resistance is suspected, retreatment should be with a different class than initially used. [2]

Table 7. Clinical Efficacy Studies for Scabies Treatments*

Treatment	Study Design	Time to Cure	Results	Adverse Effects
Lindane vs. permethrin vs. benzyl benzoate[12]	Not blinded	3 weeks	Lindane 92%, permethrin 100%, benzyl benzoate 100%. Lindane less effective ($p < 0.025$).	BB had more immediate (22%) and late (42%) adverse effects
Lindane vs. permethrin[13]	Multicenter, randomized	1 month	Lindane 86%, permethrin 91%	No difference between treatments
Lindane vs. permethrin[14]	Randomized	1 month	Lindane 65%, permethrin 91%, Lindane less effective ($p < 0.025$).	None
Permethrin vs. crotamiton[15]	Randomized	1 month	Permethrin 89%, Crotamiton 60%, Crotamiton less (effective $p < 0.002$).	None
Lindane vs. permethrin vs. crotamiton[16]	Randomized	1 month	Lindane 84%, permethrin 98%, crotamiton 88%, Lindane and crotamiton less (effective $p < 0.025$).	No difference between treatments
Ivermectin vs. lindane[17]	Randomized, prospective, controlled, double-blind	1 month	Ivermectin 95%, lindane 96%	No significant adverse effects
Ivermectin vs. lindane[18]	Randomized	1 month	Ivermectin 83%, lindane 44%	One severe headache from ivermectin
Ivermectin vs. permethrin[19]	Randomized	2 weeks	Ivermectin 95%, permethrin 98%	Not discussed

*Adapted from Reference 1.

Table 8. Clinical Efficacy Studies for Pediculosis Treatments*

Treatment	Study Design	Time to Cure	Results	Adverse Effects
Lindane vs. permethrin (head lice)[20]	Randomized	1 week	Lindane 85%, permethrin 99% ($p<0.001$)	No difference between treatments
Permethrin vs. placebo with lindane comparison group Head lice)[21]	Randomized, lindane comparison group	1 week	Lindane 43%, permethrin 97%, placebo 6%, (Per vs. placebo $p< 0.001$)	No difference between treatments
Lindane vs. permethrin (head lice)[22]	Randomized	1 week	Lindane 76%, permethrin 98% ($p<0.001$)	No difference between treatments
Lindane vs. Permethrin (pediculosis pubis)[23]	Randomized	1 week	Lindane 60%, permethrin 57%	No difference between treatments
Lindane vs. pyrethrins (head lice)[24]	Randomized	1 week	Lindane 88%, pyrethrins 95%	None
Permethrin vs. pyrethrins(head lice)[25]	Alternating treatments	1 week	Permethrin 96%, pyrethrins 45%	None
Permethrin vs. pyrethrins (head lice)[26]	Randomized	1 week	Permethrin 98%, pyrethrins 85%	More skin problems after treatment failure with permethrin
Malathion vs. combing (head lice)[27]	Not blinded	1 week	Malathion 78%, combing 38%	Not discussed
Permethrin vs. Bactrim or both (head lice)[28]	Randomized	1 month	Permethrin 72%, Bactrim 78%, both 92.5%	3 Bactrim-related rashes, no major adverse effects

*Adapted from Reference 1.

Additional Evidence

Dose Simplification: Little peer reviewed data was found in a literature search of Medline/Pubmed and Ovid on adherence with different treatments for pediculosis and scabies. Some dermatologists suggest most treatment failures are not a result of poor compliance, but due to growing resistance to insecticides.[29]

Stable Therapy: Not Applicable.

Impact on Physician Visits: No peer reviewed data was found in a literature search of Medline/Pubmed or Ovid.

IX. Conclusions

A number of effective topical scabicide and pediculocide treatments are available. Permethrin products are recommended as first-line therapy for treatment of scabies and lice. Generic alternatives are available for the permethrin products (e.g. Acticin) and Nix is available over-the-counter. Both of these products are preferred and are covered. Lindane, a well known older agent has been relegated to second line therapy due to risk of toxicity. Other available agents offer alternative options (in different chemical classes) should a resistant case occur.

The permethrin products within this class offer significant clinical advantage in general use over the other brands, generics and OTC products in the same class, but are comparable to each other. Additionally, lindane possesses an extensive adverse effect profile.

X. Recommendations

Because generic and over-the-counter permethrin products are available, no brand of permethrin is recommended for preferred status. At this time, no brand lindane product is available; however, should one become available, it should not be placed in preferred status regardless of cost.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Miscellaneous Local Anti-infectives
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I. Overview

Miscellaneous local anti-infectives are indicated for a variety of uses, depending on the specific product. The agents reviewed in this monograph can be used for umbilical cord care, burn treatment, vaginal infections, and antiseptic cleansing. Table 1 contains a list of the products that will be included in this AHFS class review. This review encompasses all dosage forms and strengths.

Table 1. Miscellaneous Local Anti-infectives Included in this Review

Rx/OTC	Generic Name	Formulation	Example Brand Name (s)
Rx	Acetic acid 0.9%/ oxyquinolone sulfate 0.025%	Vaginal gel**	Relagard, Fem pH (is a branded generic)
Rx	Acetic acid 0.9%/ oxyquinolone sulfate 0.025%/ ricolinic acid 0.7%	Vaginal gel**	Aci-Jel, Acid Jelly
OTC	Chlorhexidine gluconate	Dressing Wipes** Solution/Liquid* Sponge/Brush	Biopatch (1"/4mm, 1"/7mm, ¾"/1.5mm) Hibistat Towelettes Hibistat Hand Rinse 0.5% (brand only), Chlorostat Skin Cleanser and Surgical Scrub 2% and 4% (brand only), Betasept Surgical Scrub 2% and 4%, Dyane Skin Cleanser 2% AND 4%, Icicles Antiseptic/Antimicrobial Skin Cleanser 4% Icicles
Rx	Hexachlorophene	Cleansing Emulsion 3%	pHisoHex
Rx	Mafenide acetate	Cream 8.5%	Sulfamylon
Rx	Ammoniated mercury 5% (with salicylic acid 2.5%)	Lotion	Emersal
Rx	Nitrofurazone	Solution 0.2%**, Cream 0.2%, Ointment 0.2%**	Furacin
Rx	Silver nitrate*	Ointment 10%, Solution 0.5%, 10%, 25%, 50%, Applicators	Silver nitrate
Rx	Silver sulfadiazine	Cream 1%**	Silvadene, Thermazene,
Rx	Sulfanilamide	Vaginal Cream 15% and Suppositories 1.05gm	AVC

*As of 2004, silver nitrate is classified in AHFS class 520492 (Miscellaneous anti-infectives).
**Generic Available.

II. Current Treatment Guidelines

Umbilical Cord Care

The umbilical cord is a site for bacterial colonization, which may lead to cord stump infections in neonates. Because of this, some practitioners believe antiseptic use is warranted.[1,2,3] It is not standard of practice in all cases because of a delay in cord detachment. Generally, preterm infants are most at risk for developing infections secondary to their prematurity and are at higher risk for nosocomial infections (due to longer hospital stays), therefore, antiseptic use is considered for these patients.[1,2]

Chlorhexidine, tincture of iodine, povidone-iodine, triple dye, and silver sulfadiazine have shown to be the most effective in preventing stump infection. Choice of an agent is dependant on the predominant flora, which is typically *S. aureus*. Table 2 summarizes the advantages and disadvantages of these agents.[1]

Table 2. Advantages and Disadvantages of Cord Care Treatments[1]

Drug	Advantages	Disadvantages
Chlorhexidine gluconate	Good persistent effect, low toxicity	Expensive
Tincture of iodine	More effective than iodophors (e.g. povidone-iodine)	Mild suppression of thyroid function (reversible)
Povidone-iodine	Effective, short cord separation time	Mild suppression of thyroid function (reversible), allergic reactions may occur
Triple dye	Effective	Increases cord separation time, stains skin and clothing, ineffective against group B hemolytic streptococci
Silver sulfadiazine	Good persistent effect	Bacterial resistance to sulfonamides may occur, allergic reaction (1%)

Burn wound care

Burn patients are predisposed to infection due to the loss of the protective barrier function of the skin, which leads to the entry of microorganisms and induces systemic immunosuppression. Complications secondary to infections are the major cause of morbidity and mortality in patients with severe burns. Closure and healing of the wound are the major goals of burn wound management. Excision of burned tissue and debridement of necrotic tissue, as well as grafting of skin or skin substitutes, have shown to reduce mortality.[4,5]

Topical anti-infective agents are useful for decreasing the bacterial burden of burn wounds, thus minimizing the incidence of infection.[4,5] Prior to the use of topical anti-infectives, the overall mortality of burn patients was approximately 38-45%. After the introduction of these agents to clinical practice, the rate decreased to 14-24%.[6] *Streptococci* and *staphylococci* are the main organisms involved in burn wound infections. *Pseudomonas* and fungi have also emerged as pathogens in involved in burn infections due to the growing use of wide spectrum antibiotics.[4,5]

The three most commonly used topical anti-infectives in burn management are silver sulfadiazine, mafenide acetate and silver nitrate. All three of these agents have a broad spectrum of activity, which includes many bacteria and some fungi.[4] The initial agent typically used is silver sulfadiazine. If bacteria resistance occurs, mafenide acetate is then used. In addition to its broader spectrum of activity (including *Pseudomonas*), mafenide acetate is beneficial because of its ability to penetrate eschars. The reason it is not considered first line is because of its adverse effects.[5] Nitrofurazone is another topical anti-infective agent that is used in burn treatment.[6]

Silver nitrate solution delivered in occlusive dressings may be an effective option in patients with an allergy to sulfonamides or those who develop a hypersensitivity to one of the other agents. Because it does not penetrate the eschar due to precipitation upon contact with the exudates, silver nitrate is only beneficial for providing a barrier to minimize infection. It is not effective in treating wound infections.[5]

III. Indications of the Miscellaneous Local Anti-infectives

a. **Acetic acid/oxyquinolone sulfate with or without ricolinic acid** is used as an adjunctive therapy in those cases where restoration and maintenance of vaginal acidity is desirable (e.g. bacterial vaginosis).

b. **Chlorhexidine gluconate** is available in multiple formulations.[1-3, 7-8] Chlorhexidine gluconate is useful for its antiseptic activity and rapid, long-lasting antibacterial effect. It is effective against gram-positive and gram-negative bacteria, including *Pseudomonas aeruginosa* and *Chlamydia trachomatis*, certain fungi, and certain viruses. Chlorhexidine is indicated for use as an anti-infective skin cleanser for surgical hand antisepsis, preoperative skin preparation, disinfection prior to insertion of catheters, routine hand washing in health care professionals, and skin wound and general skin cleansing. Chlorhexidine gluconate is also available as oral mouth care products for the treatment of gingivitis, however, these products (Peridex, PerioGard and PerioChip) are classified in AHFS class 520492, and therefore, are not part of this review.

c. **Hexachlorophene** (pHisoHex®) is an antisudsing emulsion that is indicated for use as a bacteriostatic skin cleanser and surgical scrub. It may also be used to control an outbreak of gram-positive infection when other procedures have not been successful. A cumulative antibacterial effect occurs when used repeatedly.[9]

d. **Mafenide acetate** (Sulfamylon®) is available as a cream and topical solution. The cream is indicated as adjunct therapy in the treatment of second- and third-degree burns, while the solution is indicated as adjunct therapy to control the bacterial infection of burn wounds.[10, 11]

e. **Ammoniated mercury**, available as a cream, is indicated for impetigo, psoriasis, minor skin infections and other skin disorders. Because of the toxicity associated with topical ammoniated mercury, this product is rarely used.[12]

f. **Nitrofurazone** is indicated as adjunct therapy for second and third degree burns when bacterial resistance is an issue. It is also indicated for skin grafts when bacterial contamination may cause graft rejection or donor site infection.[7]

g. **Silver nitrate** solution is used as adjunct therapy in the prevention of burn wounds infections.[4,5]

h. **Silver sulfadiazine** is indicated as an adjunct for the prevention and treatment of wound sepsis in second- and third-degree burn. It has broad antimicrobial activity and is bactericidal against many gram-negative and gram-positive bacteria, as well as against yeast. Patients allergic to sulfonamides may also be allergic to silver sulfadiazine.[13, 14]

i. **Sulfanilamide** (AVC™) is an anti-infective agent used in the management of vulvovaginitis caused by Candida albicans. [15] In addition to sulfanilamide, the product AVC™ used to contain aminacrine hydrochloride and allantoin. In this former combination, the product was an alternative therapy for trichomoniasis.[19]

IV. Pharmacokinetics of the Miscellaneous Local Anti-infectives[8-18]

(data is limited, only some information can be found in package inserts)

Acetic acid/oxyquinolone sulfate with or without ricolinic acid – Systemic absorption of either product is minimal or in certain cases undetected.

Chlorhexidine gluconate – bacteriostatic or bactericidal in action depending on the concentration. Chlorhexidine becomes adsorbed onto cell surfaces of susceptible organisms and results in increased permeability. The anti-infective activity of chlorhexidine varies depending on pH; the drug is most active at a neutral or slightly acidic pH (e.g. 5.5-7).[12] Unlike iodine, the anti-infective activity of chlorhexidine is not reduced by the presence of organic matter such as blood.

Hexachlorophene – absorbed rapidly through the skin. Repeated daily application results in a residual of the drug being retained on the skin for several days. One study has shown hexachlorophene is absorbed systemically (3%) following topical application.[12] In adults, 3-4 weeks of daily total body bathing with a 3% hexachlorophene preparation reportedly results in serum concentrations of the drug as high as 1.42mcg/ml. In animals, characteristic changes in the CNS associated with this drug's toxicity occur at serum drug concentrations of about 1mcg/ml or greater. The half-life of the drug in 6 infants was reported to be 6.1-44.2 hours.

Mafenide acetate – diffuses through devascularized areas, is absorbed and converted to inactive metabolite, which is cleared via the kidneys. The amount of drug absorbed is proportional to the size of the burn being treated.

Ammoniated mercury – the kinetic parameters of ammoniated mercury have not been fully characterized, the drug is absorbed and excreted in urine following topical application. Reports of systemic adverse effects, including mercury poisoning, following topical application of the drug indicate it is absorbed.

Silver sulfadiazine – absorption varies depending on body surface area and amount of tissue damage. Silver sulfadiazine itself is not absorbed, it reacts slowly with sodium chloride, sulfhydryl groups, and protein, resulting in the release of sulfadiazine. The sulfadiazine component may be absorbed from the application site, particularly when applied to second-degree burns.

V. Drug Interactions of the Miscellaneous Local Anti-infectives [8-18]

Table 3. Drug Interactions

Generic Name	Interacting Drug (Effect)
Acetic Acid/oxyquinolone sulfate with or without ricolinic acid	– None documented
Chlorhexidine gluconate	*
Hexachlorophene	*
Mafenide acetate	*
Ammoniated mercury	– Topical iodine-containing products (increased toxicity) – Topical sulfur-containing preparations (chemical reaction releasing hydrogen sulfide, which may be irritating and stain the skin black)
Nitrofurazone	*
Silver nitrate	*
Silver sulfadiazine	*
Sulfanilamide	– None documented

*Not documented in package insert, product information, or reference text.

VI. Adverse Drug Events with the Miscellaneous Local Anti-infectives [8-18]

Table 4. Adverse Drug Events

Generic name	Adverse effect
Acetic Acid/oxyquinolone sulfate with or without ricolinic acid	Occasional cases of local stinging and burning have been reported.
Chlorhexidine gluconate	*
Hexachlorophene	Dermatitis, photosensitivity, mild scaling or dryness, lesions in white matter of brain, CNS effects
Mafenide acetate	Pain or burning sensation, rash, pruritis, erythema, facial edema, swelling, hives, blisters, eosinophilia, skin maceration from prolonged wet dressings, tachypnea, hyperventilation, decrease in pCO2, metabolic acidosis, increase in serum chloride
Ammoniated mercury	Mercury poisoning (symptoms include albuminuria, headache, gingivitis, erythroderma, nausea, dizziness, precordial pain, contact dermatitis, conjunctivitis, epistaxis, keratitis, tremor, neuritis, hematologic abnormalities, metallic taste and purpura)
Nitrofurazone	Contact dermatitis
Silver nitrate	Cytotoxic; transeschar leaching of sodium, potassium, chloride, and calcium
Silver sulfadiazine	Leukopenia, skin necrosis, erythema multiforme, skin discoloration, burning sensation, rashes, interstitial nephritis
Sulfanilamide	Burning sensation

*None documented in product information.

VII. Dosing and Administration of the Miscellaneous Local Anti-infectives [8-18]

Acetic Acid/oxyquinolone sulfate with or without ricolinic acid
The usual dose is one applicatorful, administered intravaginally, morning and evening. Duration of treatment may be determined by the patient's response to therapy.

Chlorhexidine gluconate
Chlorhexidine gluconate 2 and 4% solutions in a sudsing base (skin cleanser) and chlorhexidine gluconate 0.5% solution in an alcohol base with emollients are applied topically to the skin and hands. Chlorhexidine gluconate solutions in a sudsing base should not be used for preoperative skin preparation on the face of head. Dressings containing the drug (20%) are applied topically at the site of vascular and nonvascular percutaneous devices.[2, 3, 12]

Hexachlorophene
Hexachlorophene is applied topically to the skin in a concentration of 3%. Is should not be applied to mucous membranes.

Surgical hand scrub - Wet hands and forearms with water. Apply approximately 5ml over the hands and rub into a copious lather by adding small amounts of water. Spread suds over hands and forearms and scrub well with a wet brush for 3 minutes. Pay particular attention to the nails and interdigital spaces. A separate nail cleaner may be used. Rinse thoroughly under running water. Repeat, then dry.

Bacteriostatic cleansing - Wet hands with water. Apply approximately 5ml into the palm, work up a lather with water and apply to area to be cleansed. Rinse thoroughly.

Mafenide acetate
Sulfamylon® 8.5% Cream
Apply 1/16 inch thickness of cream once or twice daily on cleansed and debrided skin area.

Ammoniated mercury
Emersal® (ammoniated mercury 5% with salicylic acid 2.5%)
Ammoniated mercury has been applied topically once or twice daily as lotions or ointments containing 5 or 10% of the drug.

Nitrofurazone
Apply directly to wound area or on gauze. Reapply once daily or every few days, depending on dressing.

Silver nitrate
Apply on gauze dressings. Change dressings two to three times daily and moisten every two hours.

Silver sulfadiazine
Apply 1/16 inch thickness of 1% cream once to twice daily on cleansed and debrided skin area.

Sulfanilamide
One applicatorful or one suppository once or twice daily. Treatment typically for 30 days.

Special Dosing Considerations

- Mafenide: Safe use of mafenide during pregnancy has not been established. Use is not recommended for treatment in women of childbearing potential unless the burn area covers more than 20% of the body surface or the therapeutic benefits to the patient justify the possible risks to the fetus. Use of mafenide cream in pediatric patients is the same as in adults, and the usual precautions and contraindications should be observed.
- Ammoniated Mercury: Should not be used in children, since it may cause acrodynia.
- Silver Sulfadiazine: Because sulfonamide therapy has produced kernicterus in neonates, silver sulfadiazine cream is contraindicated in premature neonates or neonates younger than 2 months of age. Silver sulfadiazine is not recommended for use in pregnant women unless the burned area covers more than 20% of the body surface or the therapeutic benefits to the patient outweigh the possible risks to the fetus.

VIII. Effectiveness of the Miscellaneous Local Anti-infectives

Recent research data is lacking on most of the addressed topical anti-infectives, because of the age of the agents. The agents in this class are either part of standard treatment (e.g. burn therapy) or not typically used in general practice (e.g. ammoniated mercury, sulfanilamide).

Additional Evidence

Dose Simplification: Not Applicable.

Stable Therapy: The treatments in this class are for very specific conditions. Some are available OTC and as generics, and some are used in acute care situations. In addition, due to the non-systemic nature of many of these topical agents, it is unlikely that a switch in treatment might result in significant impact to the patient.

Impact on Physician Visits: No peer reviewed data was found in a literature search of Medline/Pubmed and Ovid.

IX. Conclusions

The products in this AHFS therapy class are important to the care of burn patients. The remaining products in this class are used for varying indications. At this time, there are generic alternatives available in the nitrofurazone solution and ointment, silver sulfadiazine cream, some of the chlorhexadine products, and the acetic acid/oxyquinolone sulfate with or without ricolinic acid products. Therefore, all brand products within the miscellaneous local anti-infectives class reviewed are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

X. Recommendations

No brand miscellaneous local anti-infective is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of the Topical Anti-inflammatory Agents
AHFS 840600
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I. Overview

Millions of people are affected annually with skin diseases that cause marked discomfort, significant morbidity, and rarely death. Topical corticosteroids are extremely useful in the treatment of symptomatic relief of inflammatory dermatoses. When possible, the cause of the dermatoses should be determined and eliminated. Although systemic corticosteroids are more effective in most dermatologic inflammations, topical treatment is preferred in most responsive cases because it causes fewer adverse systemic effects.[1] Corticosteroids play an important role in dermatology because of their anti-inflammatory and immunosuppressive effects and also their anti-proliferative effects on keratinocytes.[2]

Since the introduction of hydrocortisone in the early 1950s, treatment with topical corticosteroids has revolutionized dermatology. The primary vasoconstrictor assay is the method used to classify the potency of topical steroids, one of the ways to differentiate the drugs in this class, that also correlates with clinical efficacy.[2] The efficacy and possible adverse effect profiles depend on the steroid type and the vehicle, the application method, the nature and extent of the skin disease, and specific patient factors such as age and site of the disease.

Topical corticosteroids are generally most effective in the treatment of acute or chronic dermatoses such as seborrheic or atopic dermatitis, localized neurodermatitis, anogenital pruritus, psoriasis, and the inflammatory phase of xerosis.[1] Topical corticosteroids are effective in the late phase of allergic contact dermatitis, but systemic corticosteroids are usually required to relieve the acute manifestations of these dermatoses.

The topical anti-inflammatory drugs are classified by their potency. Table 1lists the drugs in this review. This review encompasses all topical dosage forms and strengths.

Table 1. Products in this Review

Group**	Generic Name	Formulation	Example Brand Name (s)	Rx/OTC
VI	Alclometasone dipropionate 0.05%	Cream Ointment	Aclovate	Rx
II	Amcinonide 0.1%	Ointment*, Lotion*, Cream*	Cyclocort	Rx
II Ointment 0.05% III Cream 0.05% V Lotion 0.05%	Betamethasone dipropionate 0.05%	Cream*, Ointment*, Lotion* Aerosol (0.1% only)	Maxivate, Diprosone, Alphatrex	Rx
I Cream or ointment 0.05% (Diprolene/AF)	Augmented betamethasone dipropionate 0.05%	Ointment*, Cream*, Gel, Lotion	Diprolene, Diprolene AF	Rx
III Ointment 0.1% V Cream or lotion 0.1%	Betamethasone valerate 0.05%, 0.1%	Cream* Ointment* (0.1% only) Lotion* (0.1% only) Foam 1.2mg/g	Luxiq, Beta-Val, Betatrex	Rx

I Cream, foam or ointment 0.05%	Clobetasol propionate/ emollient 0.05%	Ointment*, Cream*, Lotion, Scalp Application, Gel*, Foam	Temovate, Temovate Emollient, Olux (foam only), Embeline, Embeline E, Cormax, Clobex, Clobevate	Rx
III	Clocortolone pivalate 0.1%	Cream	Cloderm	Rx
VI	Desonide 0.05%	Cream* Ointment* Lotion*	Lokara, Desowen, Delonide, Tridesilon	Rx
II Cream or ointment 0.25%, gel 0.05% IV Cream 0.05%	Desoximetasone	Ointment* (0.25%) Cream* (0.05 and 0.25%) Gel* (0.05%)	Topicort, Topicort LP	Rx
I Ointment 0.05% (Psorcon) II Ointment 0.05% (Florone, Maxiflor) III Cream 0.05% (Florone, Maxiflor)	Diflorasone diacetate/emollient 0.05%	Cream* Ointment*	Psorcon, Psorcon E, Maxiflor, Apexicon, Apexicon A	Rx
IV Cream 0.2%, Ointment 0.025% V Cream 0.025% VI Solution 0.01%	Fluocinolone acetonide 0.025%, 0.01%	Cream*, Ointment*, Solution* 0.2% Cream Shampoo Oil	Synalar, Synalar HP, Derma-Smooth/FS, Capex Shampoo	Rx
II Cream, Ointment or gel 0.05%	Fluocinonide/emollient 0.05%	Cream*, Ointment*, Solution*, Gel*	Lidex, Lidex-E, Dermacin	Rx
IV Ointment 0.05% V Cream 0.05%	Flurandrenolide 0.05%	Ointment, Cream, Lotion*, Tape	Cordran, Cordran SP, Cordran Tape Patch	Rx
III	Fluticasone propionate	0.05% Cream* 0.005% Ointment*	Cutivate	Rx
II Cream 0.1%	Halcinonide / emollient 0.025%, 0.1%	Cream Ointment Solution	Halog, Halog-E (0.1% cream only)	Rx
I	Halobetasol Propionate 0.05%	Cream Ointment	Ultravate	Rx
VI	Hydrocortisone 0.2%, 0.5%, 1%, 2% (lotion only), 2.5%	Cream*, Ointment*, Lotion*, Liquid*, Gel*, Solution*, Spray, Stick roll on*	Texacort, Scalp-Aid, Scalp, Scalp Cort, SB hydrocortisone, Sarnol HC, Rederm, Recort Plus, Nutracort, Nupercainal HC, Lacticare HC, Instacort – 10, Hytone, Hycort, Hydro lotion, Dr. Smith's Anti-itch, Dermolate Anti-itch, Cortaid, Cetacort, Beta HC, Aquanil HC	Rx and OTC, depending on labeling
VI	Hydrocortisone / aloe 0.5%, 1%	Cream*, Ointment*	Hydrocortisone	OTC
VI	Hydrocortisone acetate 0.5% and 1%	Cream* Ointment*	Medi-cortisone, Cortane, Cortaid	OTC (1% Cream may be Rx or OTC)

V Cream 0.1%	Hydrocortisone butyrate/ emollient 0.1%	Cream Ointment Solution	Locoid	Rx
VI	Hydrocortisone acetate / aloe 0.5%	Cream*, Ointment* Paste	Cortaid w/Aloe	OTC
IV Potency Indicated Per Manufacturer	Hydrocortisone probutate 0.1%	Cream	Pandel	Rx
-	Hydrocortisone sodium phosphate	Injection	Hydrocortone	Rx
V Cream 0.2%	Hydrocortisone valerate 0.2%	Cream* Ointment	Westcort	Rx
III Ointment 0.1%	Mometasone furoate 0.1%	Ointment* Cream Lotion	Elocon	Rx
V Cream 0.1% (emollient)	Prednicarbate 0.1%	Cream Ointment	Dermatop	Rx
III Cream 0.5% IV Ointment 0.1% V Cream 0.1%, Lotion 0.1%	Triamcinolone acetonide 0.025%, 0.1%, 0.5%	Cream* Ointment* Lotion* (0.025 and 0.1% only) Paste* 0.1% Spray	Kenalog, Kenalog in orabase, Cinalog, Aristocort HP, Aristocort A, Aristocort	Rx

*Generic Available.
**Relative activity in decreasing order, from I to V (I is most potent, VI is least potent). Preparations in each group are approximately equivalent.

II. Current Treatment Guidelines

The American Academy of Dermatology has issued practice guidelines for the use of topical corticosteroids and specifically for use in atopic dermatitis. Tables 2 and 3 further detail the recommendations.

Table 2. Guidelines of Care for the Use of Topical Glucocorticosteroids[2]

American Academy of Dermatology
Choice of Vehicle The selection of a topical corticosteroid in terms of strength and vehicle depends on the nature, location, and extent of the skin lesion(s), the age of the patient, and the duration of treatment. **Ointments** Ointments are generally most effective for treating thick, fissured, lichenified skin lesions. The occlusive nature of the vehicle enhances corticosteroid penetration. However, some patients may consider ointments aesthetically undesirable. **Creams** Creams are generally the vehicle of choice for acute and subacute dermatoses. They can be used on moist areas of the skin and are more aesthetically acceptable to patients. Some creams may be drying, and patients may benefit from application of a moisturizer in addition to the corticosteroid cream. **Solutions, gels, and sprays** These vehicles are the most aesthetically elegant for use on the scalp. They are also useful when a non-oil-based vehicle is desirable. **General Use** • Thin, acute, inflammatory lesions frequently respond to low-medium strength topical corticosteroids. • Chronic, hyperkeratotic, lichenified, or indurated lesions may respond only to high-very-high strength topical corticosteroid preparations. • Low-strength preparations are preferred for the face and intertriginous areas. • Short-term (2 weeks) use of more potent agents is occasionally required, however, these agents should rarely be used in the diaper area of infants. • Recalcitrant lesions of the face such as those of discoid lupus erythematosis and lichen sclerosis may require more potent corticosteroids and a longer duration of treatment. Treatment of the soles and palms often requires a high or very high strength agent to achieve significant improvement. • Due to risk of systemic absorption, corticosteroids of low to medium strength are preferred when large areas are to be treated. • The duration of use of very high strength topical agents should not exceed 3 weeks. • Topical corticosteroids should be discontinued when the skin disease has resolved. When long-term use is required, patients should be monitored for loss of clinical effect over time. • Continuous long-term treatment near puberty should be avoided.

Table 3. Guidelines of Care for Atopic Dermatitis[3]

American Academy of Dermatology
Definition: Atopic dermatitis is a chronic inflammatory pruritic skin disease that occurs most frequently in children but can occur in adults and follows a relapsing course. It is often associated with elevated serum IgE levels and a personal or family history of Type I allergies, allergic rhinitis and asthma. **Treatment Recommendations** • Topical corticosteroids are the standard of care to which other treatments are compared. • Cutaneous complications such as striae, atrophy, and telangiectasia limit the extensive use of these agents. • Despite extensive use of topical corticosteroids, there are limited data regarding optimal corticosteroid concentrations, duration and frequency of therapy and quantity of application. Similarly, data supporting the perception that long term corticosteroid use is not associated with extracutaneous adverse effects are lacking. • Altering the local environment by hydration and/or occlusion as well as by varying the vehicle can impact the absorption and effect of the topical corticosteroid administered. • Tachyphylaxis (loss of clinical effect over time) is a clinical concern, but there is no experimental documentation. • The use of long-term intermittent application of corticosteroids appears helpful and safe in two randomized controlled studies. More independent studies of other formulations are needed. **Other Topical Therapies** • Emollients are a standard of care, are steroid sparing and useful for both prevention and maintenance therapy. • Calcineurin inhibitors, pimecrolimus and tacrolimus have been shown to reduce the extent, severity, and symptoms of atopic dermatitis in adults and children. • Tar products may be associated with therapeutic benefits, but is limited by compliance. • Short-term adjunctive use of topical doxepin may aid in the reduction of pruritus, but the development of side effects may limit usefulness.

III. Comparative Indications of the Topical Anti-inflammatory Agents

Following topical application, the corticosteroids produce anti-inflammatory, antipruritic, and vasoconstrictor actions. Table 4 illustrates the Food and Drug Administration approved indications for each agent.

Table 4. FDA-Approved Indications for the Topical Anti-inflammatory Agents[1, 4, 5]

Agent	Inflammatory and Pruritic Dermatoses	Plaque Psoriasis	Dermatoses of the Scalp	Self Medication (OTC)	Oral inflammatory or ulcerative lesions from trauma
Alclometasone dipropionate	✓				
Amcinonide	✓				
Betamethasone dipropionate	✓				
Aug. betamethasone dipropionate	✓				
Betamethasone valerate	✓				
Clobetasol propionate	✓	✓	✓		
Clocortolone pivalate	✓				
Desonide	✓				
Desoximetasone	✓				
Diflorasone diacetate	✓				
Fluocinolone acetonide	✓				
Fluocinonide	✓				
Flurandrenolide	✓				
Fluticasone propionate	✓				
Halcinonide	✓				
Halobetasol Propionate	✓				
Hydrocortisone	✓			✓	
Hydrocortisone / aloe	✓			✓	
Hydrocortisone acetate	✓			✓	✓ (Paste)
Hydrocortisone butyrate	✓				
Hydrocortisone acetate / aloe	✓			✓	
Hydrocortisone probutate	✓				
Hydrocortisone valerate	✓				
Mometasone furoate	✓				
Prednicarbate	✓				
Triamcinolone acetonide	✓				✓ (Paste)

Hydrocortisone and hydrocortisone acetate nonprescription preparations containing 0.5% and 1% are used for the temporary relief of minor skin irritations, itching, and rashes caused by eczema, dermatitis, insect bites, poison ivy, poison oak, poison sumac, soaps, detergents, cosmetics, or jewelry. They can also be used for the temporary relief of itchy anal and/or genital areas, and for temporary relief of itching and minor scalp irritation caused by scalp dermatitis. Hydrocortisone acetate, probutate, butyrate, and valerate esters can also be used for dermatoses of the anogenital area.

IV. Pharmacokinetic Parameters of the Topical Anti-inflammatory Agents

The pharmacokinetics of corticosteroids varies among individuals and can be increased with use of occlusive dressings. Use of different vehicles also can cause varying penetration of the drug. Pharmacokinetic data for the topical corticosteroids is applicable to the class of drugs as a whole. Specific information for some of the individual products is not available.

Following topical administration of corticosteroids to most areas of normal skin, only minimal amounts of the drug reached the dermis and entered systemic circulation.[1] It is important to remember that absorption is markedly increased when the skin has lost its keratin layer and can be increased by inflammation and/or diseases of the epidermal barrier. Corticosteroids are absorbed to a greater degree from the scrotum, axilla, eyelid, face, and scalp than from the forearm, knee, elbow, palm, and sole. Topical application of corticosteroids to the mucosa of the genitourinary or lower intestinal tract may result in substantial systemic absorption of the drugs. Following topical absorption, corticosteroids enter the systemic circulation and are metabolized in the liver and excreted primarily via the kidneys, and in some cases, the feces.

Table 5 lists the available pharmacokinetic information for the topical corticosteroids.

Table 5. Pharmacokinetic Parameters of the Anti-inflammatory Agents[1, 4, 5]

Agent	Absorption	Distribution	Metabolism /Elimination
Alclometasone dipropionate	Varies with vehicle and can be increased with occlusive dressings; 3% of drug reaches systemic absorption.	-	Renal and Feces
Amcinonide	-	-	-
Betamethasone dipropionate	-	-	-
Aug. betamethasone dipropionate	One study of Diprolene AF showed the drug caused a slight lowering of adrenal corticosteroid secretion	-	-
Betamethasone valerate	-	-	-
Clobetasol propionate	Mean plasma levels peaked in 10 hours and were higher in patients with psoriasis or eczema	Not fully quantified	Renal and feces
Clocortolone pivalate	-	-	-
Desonide	-	-	-
Desoximetasone	-	-	-
Diflorasone diacetate	-	-	-
Fluocinolone acetonide	-	-	-
Fluocinonide	-	-	-
Flurandrenolide	-	-	-
Fluticasone propionate	Plasma levels are below the level of quantification; one study with occlusive dressings resulted in plasma levels of 0.07-0.39ng/mL.	91% protein bound, Metabolized in the liver by CYP450 3A4	Terminal half-life of 7.2 hours
Halcinonide	-	-	-
Halobetasol Propionate	-	-	-
Hydrocortisone	-	-	-
Hydrocortisone / aloe	-	-	-
Hydrocortisone acetate	-	-	-
Hydrocortisone butyrate	-	-	-
Hydrocortisone acetate / aloe	-	-	-
Hydrocortisone probutate	-	-	-
Hydrocortisone valerate	-	-	-
Mometasone furoate	2-6% of dose reaches systemic circulation	Not fully quantified	Renal and feces
Prednicarbate	-	-	-
Triamcinolone acetonide	-	-	-

V. Drug Interactions with the Topical Anti-inflammatory Agents

In general, topical application of corticosteroids to the skin does not provoke clinical evidence of systemic absorption. Therefore, it is unlikely that use of a topical corticosteroid would result in clinical drug interactions. More caution should be used in those patients using topical corticosteroids on large areas of the body, for prolonged periods of time, with an occlusive dressing, and/or in infants and children or when potent agents (Group I) are used. In addition, drug interactions with the topical anti-inflammatory agents are not documented throughout the literature.

VI. Adverse Drug Events of the Topical Anti-inflammatory Agents

In general, adverse events for the topical corticosteroids occur similarly with all drugs in the class. There are no advantages of one product compared to others. When adverse events do occur, a lower strength/potency corticosteroid can be used.

Reversible hypothalamic-pituitary-adrenal (HPA) axis suppression, manifestations of Cushing's syndrome, hyperglycemia, and glucosuria have occurred in some patients receiving topical corticosteroids. Recovery of HPA-axis function is generally prompt and complete following discontinuance of the drug. Numbness of fingers has been reported in patients receiving topical clobetasol propionate.

Local Effects
Adverse dermatologic events are more likely to occur in intertriginous and facial areas, and occur with greater frequency with use of occlusive dressings and fluorinated corticosteroids. Prolonged therapy also increases the chance for adverse dermatologic events.

Common adverse events with topical corticosteroids include atrophy of the epidermis, subcutaneous tissue, and dermal collagen and drying and cracking or tightening of the skin.[1] Epidermal thinning, telangiectasia, increased fragility of cutaneous blood vessels, purpura, and atrophic striae may also occur. Other less common adverse events include acneiform eruption, vesiculation, irritation, pruritus, hypertrichosis, rosacea-like eruptions on the face, erythema, hyperesthesia, perioral dermatitis, burning or stinging sensation, folliculitis, and hypopigmentation. Skin ulceration has occurred in patients with impaired circulation who were treated with topical corticosteroids.

In addition to the other adverse events reported, maceration of the skin and miliaria may occur, especially when occlusive dressings are used. Stripping of the epidermis and purpura have occurred with flurandrenolide tape dressings. Dermatological infections may occur with topical corticosteroids and these drugs can mask the manifestations of infection.

Adverse events usually improve when the drug is discontinued, but may persist for long periods of time. It is possible for pustular rebound to occur on the face, perianal region, or genitals. Few patients require treatment with systemic antibiotics and a topical nonfluorinated corticosteroid (e.g. hydrocortisone) and/or sulfur. Allergic dermatitis occurs rarely.

VII. Dosing and Administration of the Topical Anti-inflammatory Agents

Topical corticosteroids are generally applied sparingly to the affected area 1-4 times daily. When a favorable response is achieved, the frequency of application or concentration of the corticosteroid is reduced to the minimum necessary to maintain control and avoid relapse and, if possible, the drug should be discontinued. Table 6 lists specific dosing instructions for use of the topical anti-inflammatory agents.

Table 6. Dosing for the Topical Anti-inflammatory Agents[1, 4, 5]

Agent	Availability	Dose /Frequency/Duration
Alclometasone dipropionate	Cream 0.05% Ointment 0.05%	Apply sparingly in thin films and rub gently into the affected area 2 or 3 times daily. Duration may vary from 2-6 weeks. Occlusive dressings may be used, and the duration may be longer in chronic conditions.
Amcinonide	Ointment 0.1%*, Lotion 0.1%*, Cream 0.1%*	Apply sparingly in thin films and rub gently into the affected area 2 or 3 times daily. Lotion: Apply to scalp, trunk or other affected area and rub in thoroughly twice daily. Occlusive dressings can be used for severe or resistant dermatoses.
Betamethasone dipropionate	Cream 0.05%*, Ointment 0.05%*, Lotion 0.05%*, Aerosol (0.1% only)	Should not be used with occlusive dressings. Apply sparingly in thin films and rub gently into the affected area once or twice daily.
Augmented betamethasone dipropionate	Ointment 0.05%*, Cream 0.05%*, Gel 0.05%, Lotion 0.05%	Should not be used with occlusive dressings. Because the augmented (optimized vehicle) preparations are among the most potent topical corticosteroid preparations currently available, dosage with these agents should not exceed 45g of ointment, 50g of cream, 45g of gel, or 50mL of the lotion per week. Duration should not typically exceed 2 weeks. Apply sparingly in a thin film and rub gently into the affected area once or twice daily.
Betamethasone valerate	Cream 0.05% and 0.1%*, Ointment* (0.1% only) Lotion* (0.1% only) Foam 0.12%	The foam preparation should not be used with occlusive dressings. Apply sparingly in thin films and rub gently into the affected area 1-3 times daily. Commonly, application 1-2 times daily is effective. Dosing frequency should be decreased to once daily following clinical improvement. Foam: Apply foam twice daily to the scalp, in the morning and evening.
Clobetasol propionate/ emollient	Ointment 0.05%*, Cream 0.05%*, Lotion 0.05%, Scalp Application 0.05%, Gel 0.05%*, Foam 0.05%	The cream, ointment, gel and foam are applied sparingly in thin films and rubbed gently into the affected area twice daily, in the morning and evening. The duration of treatment should generally not exceed 14 days. (up to 4 weeks for plaque psoriasis) Solution: Apply to the scalp twice daily. Dosage should not exceed 50g of the 0.05% cream, foam, or ointment or 50mL of the 0.05% solution per week. Clobetasol should not be used with occlusive dressings.
Clocortolone pivalate	Cream 0.1%	Apply sparingly in a thin film and rub gently into the affected area 1-4 times daily. Occlusive dressings may be used.
Desonide	Cream 0.05%*, Ointment 0.05%*, Lotion 0.05%*	Apply sparingly in thin films and rub gently into the affected area 2-4 times daily. Occlusive dressings may be used.
Desoximetasone	Ointment* (0.25%) Cream* (0.05 and 0.25%) Gel* (0.05%)	Desoximetasone is applied sparingly in a thin film and rubbed gently into the affected area twice daily.
Diflorasone	Cream 0.05%*	Cream: Apply sparingly in a thin film and rub gently into the affected

diacetate	Ointment 0.05%* Emollient Cream 0.05%	area 2-4 times daily. Emollient cream and ointment: Apply to the affected area 1-3 times daily. Occlusive dressings may be used with Psorcon, according to the manufacturer, however, some clinicians do not recommend use of this agent with the dressings.
Fluocinolone acetonide	0.025% and 0.01% Cream*, Ointment*, and Solution* 0.2% Cream, Shampoo 0.01%, Oil	Shampoo: Requires preparation by a pharmacist; mix the contents of the 12mg capsule with the shampoo base supplied by the manufacturer. Apply no more than 30mL of the shampoo to the scalp once daily, lather, and allowed to remain on the scalp for 5 minutes. Then rinse. The shampoo should not be used with an occlusive dressing. Cream, gel, ointment, and solution are applied sparingly in thin films and rubbed gently into the skin 2-4 times daily depending on the severity of the condition. Occlusive dressings may be used for severe or resistant dermatoses. Oil: For the treatment of atopic dermatitis in adults, fluocinolone 0.01% topical oil is applied as a thin film 3 times daily. The oil may be used in children 2 years of age and older, twice daily for no longer than 4 weeks. The oil should not be applied to the face or diaper area. Topical oil may also be applied to the scalp for psoriasis, left on with a shower cap overnight and then washed off.
Fluocinonide	Cream 0.05%*, Ointment 0.05%*, Solution 0.05%*, Gel 0.05%* Emollient cream	Apply sparingly to the affected area 2-3 times daily.
Flurandrenolide	Ointment 0.05%, Cream 0.05%, Lotion 0.05%*, Tape 0.05%	Apply sparingly in thin films and rub gently into the affected area 2-3 times daily. Occlusive dressings may be used for severe or resistant dermatoses. The tape is generally applied as an occlusive dressing to clean, dry affected areas every 12 hours.
Fluticasone propionate	0.05% Cream 0.005% Ointment	Fluticasone cream may be applied in adults and pediatric patients 3 months of age and older. (safety and efficacy in children for more than 4 weeks has not been established). Apply a thin film to the affected area once or twice (twice for the ointment) daily. Therapy should be discontinued when control is achieved. Both the cream and ointment should not be used with occlusive dressings.
Halcinonide / emollient	0.025%, 0.1% Cream, Ointment, Solution	Apply sparingly in a thin film and rub gently into the affected area 2-3 times daily. Occlusive dressings may be used for severe or resistant dermatoses.
Halobetasol Propionate	Cream 0.05% Ointment 0.05%	Apply a thin layer of cream or ointment to the affected skin once or twice daily and rub gently. Treatment should be limited to 2 weeks, and amounts greater than 50 g/wk should not be used. Therapy should be discontinued when control is achieved. Halobetasol should not be used with occlusive dressings.
Hydrocortisone 0.2%, 0.5%, 1%, 2% (lotion only), 2.5%	Cream*, Ointment*, Lotion*, Liquid*, Gel*, Solution*, Spray, Stick roll on*	Apply sparingly in a thin film and rub gently into the affected area 1-4 times daily. For treatment of the scalp, lotion should be applied directly to the affected area and rubbed into the skin gently. The lotion should not be immediately rinsed out of the hair. The aerosol spray may also be applied to the scalp. Occlusive dressings may be used for severe or resistant dermatoses. A small amount of 0.5% paste can be pressed to lesions in the mouth while developing a thin film over the area. The paste should be applied 2-3 times daily after meals and at bedtime. OTC Use

		Patients should not self-medicate with OTC preparations for longer than 7 days and these products should not be used in children younger than 2 years of age unless directed by a physician.
Hydrocortisone / aloe	Cream 0.5%, 1%*, Ointment 0.5%, 1%*	Apply sparingly in a thin film and rub gently into the affected area 1-4 times daily.
Hydrocortisone acetate	Cream 0.5%, 1%* Ointment 0.5%, 1%*	Apply sparingly in a thin film and rub gently into the affected area 1-4 times daily.
Hydrocortisone butyrate	Cream 0.1%, Ointment 0.1%, Solution 0.1%, Emollient 0.1%	Apply sparingly in a thin film and rub gently into the affected area 1-4 times daily.
Hydrocortisone acetate / aloe	Cream 0.5%*, Ointment 0.5%*, Paste 0.5%	Apply sparingly in a thin film and rub gently into the affected area 1-4 times daily.
Hydrocortisone probutate	Cream 0.1%	Apply sparingly in a thin film and rub gently into the affected area 1-2 times daily.
Hydrocortisone sodium phosphate	Injection	Not for topical use. Administer via IV, IM, or SQ injection at a dose of 15-240mg/day.
Hydrocortisone valerate	Cream 0.2%*, Ointment 0.2%	Apply sparingly in a thin film and rub gently into the affected area 1-4 times daily.
Mometasone furoate	Ointment 0.1%* Cream 0.1% Lotion 0.1%	Mometasone cream and ointment should be applied sparingly in thin films and rubbed into the affected area once daily. Both vehicles have been applied twice daily. The lotion should be applied via a few drops of the lotion to the affected area once daily. Mometasone should not be used with occlusive dressings.
Prednicarbate	Cream 0.1% Ointment 0.1%	The safety and efficacy of prednicarbate cream in children younger than 1 year of age have not been established and use in this group is not recommended. The cream or ointment should be applied sparingly in a thin film and rubbed gently into the affected area twice daily. Occlusive dressings may be used for severe or resistant dermatoses, but use of these dressings may increase the risk of local and systemic adverse events.
Triamcinolone acetonide	Cream 0.025%, 0.1%, 0.5%* Ointment 0.025%, 0.1%, 0.5%* Lotion* (0.025 and 0.1% only) Paste* 0.1% Spray	Apply sparingly in thin films and rub into the affected area gently, 2-4 times daily. The 0.5% cream and 0.5% ointment should be used only in the treatment of dermatoses that are refractory to treatment with lower concentrations. The aerosol should be applied to the affected area for about 2 seconds from a distance of about 7.5-15cm 3 or 4 times daily. Occlusive dressings may be used for severe or resistant dermatoses. For use in the mouth, a small amount of 0.1% paste is pressed to the lesion at bedtime and if necessary, 2-3 times daily after meals.

Special Dosing Considerations

- Use in pediatrics: Topical corticosteroid therapy in children should be limited to the minimum amount necessary for therapeutic efficacy; chronic topical corticosteroid therapy may interfere with growth and development. Lotrisone cream is not recommended in the treatment of diaper dermatitis. In open-label studies of children who received topical corticosteroids (betamethasone dipropionate cream or ointment), adrenal suppression occurred in 14-17% of children 9-12 years of age, 23-32% of children 6-8 years of age, 29-38% of children 2-5 years of age, and 36-50% of infants 3 months to 1 year of age.
- Use during pregnancy: Potent corticosteroid use during pregnancy has been shown to be teratogenic in animals following application. Topical corticosteroids should only be used during pregnancy when the potential benefits justify the possible risks to the fetus. Reproductive studies in rats given subcutaneous dosages of clobetasol propionate up to 50mcg/kg daily have revealed an increase in the incidence of fetal resorption and a decrease in the number of living fetuses at the highest dose.

VIII. Comparative Effectiveness of the Topical Anti-inflammatory Agents

Table 7 lists important clinical efficacy comparative trials for the topical anti-inflammatory agents. As some of the agents in this class have been around for many years, clinical comparative data dates back to the late 1970's and 1980's. Recent and up-to date trials have been included below.

Table 7. Outcomes Evidence for the Anti-inflammatory Agents

Study	Sample	Duration	Results
Betamethasone valerate foam vs. betamethasone dipropionate lotion[7]	n=61	12 week treatment (20 week follow-up) randomized, controlled, multicenter, prospective trial	In evaluating the efficacy and safety of betamethasone valerate foam in patients with mild-to-moderate alopecia areata, as compared with betamethasone dipropionate lotion applied twice daily for 12 weeks: • At week 20, the hair regrowth score was 3.1 +/- 1.5 and 1.8 +/- 1.6 in the betamethasone valerate and betamethasone dipropionate groups, respectively ($P < 0.01$). • A hair regrowth score > 3 was observed in 61% of patients in the betamethasone valerate group (19/31) in comparison with 27% (8/30) in the betamethasone dipropionate group ($P < 0.03$).
0.25% and 0.05% desoxymethasone vs. 0.1% betamethasone valerate and 1% hydrocortisone cream[8]	n=96	3 week double-blind, parallel group, multi-center design trial	To evaluate the efficacy and acceptability of 0.25% and 0.05% desoxymethasone, 0.1% betamethasone valerate, and 1% hydrocortisone creams in patients with eczema, patients were randomized to one of the three treatments for a 3 week period: • The 0.25% desoxymethasone was the most effective treatment, producing the greatest degree of improvement in all clinical parameters (erythema/redness, scaling, itching, and extent of area affected). • Hydrocortisone was the least effective and 0.05% desoxymethasone was of intermediate effectiveness. • The 0.1% betamethasone produced similar results to 0.25% desoxymethasone for half the assessments; for the other half the results were similar to 0.05% desoxymethasone.
Alclometasone dipropionate 0.05% vs. hydrocortisone 1%[9]	n=34	3 week randomized, double-blind study	Alclometasone 0.05% and hydrocortisone 1% ointments were applied twice daily for three weeks to bilateral, paired eczematous lesions of children. Results showed: • Both ointments were equally effective in relieving the signs and symptoms of eczema. • After 3 weeks of therapy, improvement in the total score of ratings of the severity of signs and symptoms averaged 88% at alclometasone treated sites and 86% at hydrocortisone treated sites.
Alclometasone dipropionate cream 0.05% vs. clobetasone butyrate cream 0.05%[10]	n=43	2 week treatment, randomized, double-blind, parallel-group study	In comparing the safety and efficacy of alclometasone dipropionate cream 0.05% and clobetasone butyrate cream 0.05% in the treatment of atopic dermatitis in children: • Both treatments were effective. • At the end of the trial, average reduction in disease signs was 85% for alclometasone dipropionate-treated patients and 86% in the clobetasone butyrate-treated group. • In the global evaluation, the physician rated symptoms as cleared in 9 of 22 alclometasone dipropionate-treated patients and in 10 of 21 clobetasone butyrate-treated patients.
Amcinonide vs. betamethasone dipropionate[11]	n=34	2 week randomized, double-blind study	In comparing the efficacy and safety of amcinonide and betamethasone dipropionate ointments, applied twice daily for 2 weeks, in patients with moderate to severe psoriasis: • Significant improvement from baseline was observed with both ointments at weeks 1 and 2. • The 2 drugs showed comparable cosmetic acceptability. • Adverse reactions experienced were burning (both groups), itching (amcinonide), and stinging (betamethasone).

Fluticasone propionate 0.005% vs. betamethasone dipropionate 0.05%[12]	n=92	4 week randomized, double-blind, parallel study	To compare the safety, tolerability, and efficacy of twice daily applications of fluticasone ointment 0.005% and betamethasone ointment 0.05% in patients with moderate-to-severe eczema, patients were randomized to treatment: • Both treatments were well tolerated and showed minimal suppression of the hypothalamic-pituitary-adrenal axis. • Statistically significant improvement in the severity of each sign/symptom was found as early as 2 weeks following treatment initiation in both groups. • Both treatment groups were found to be similar following 2 and 4 weeks of therapy with regard to almost all efficacy variables (physician's gross assessment of clinical laboratory evaluations, signs and symptoms of eczema, and patients' assessment of treatment effects).
Augmented betamethasone dipropionate lotion vs. clobetasol propionate solution[13]	n=197	2 week randomized, multicenter, investigator-blinded, parallel group study	In comparing the efficacy and safety of augmented betamethasone dipropionate 0.05% lotion and clobetasol propionate 0.05% solution in the treatment of moderate-to-severe scalp psoriasis when applied twice daily for 2 weeks: • As early as 3 days after treatment, scaling and induration were improved significantly faster by betamethasone dipropionate than by clobetasol propionate. Both treatments reduced erythema and pruritus. • Patients receiving betamethasone had a significantly greater mean percent improvement in total sign/symptom scores (P< or = 0.015) at all visits and better mean global clinical response scores at the early visits (days 4 and 8) (P< or = 0.017). • At the end of the study, only mild disease was present in both groups. • Adverse events were reported by 34% and 36.4% of patients receiving betamethasone and clobetasol, respectively. • Betamethasone appears to provide a faster onset of relief for scaling and induration which may enhance patient compliance and satisfaction with treatment.
Clobetasol propionate form 0.05% vs. clobetasol cream 0.05% and solution 0.05%[14]	n=32	2 week single-blind, randomized study	To compare the quality of life, effectiveness, user satisfaction, and cost-effectiveness of 2 clobetasol regiments for the treatment of psoriasis over 14 days, patients were randomized to clobetasol foam 0.05% to the skin and scalp, or combination clobetasol cream 0.05% to the skin and clobetasol solution 0.05% to the scalp. Results indicated: • The foam formulation performed better than a cream/solution combination by several measures: 1) A greater absolute improvement in psoriasis severity was seen in the group using the foam than in the group using the cream/solution (mean decrease in PASI=5.0 vs. 3.3, P=.05), 2) The Psoriasis Area and Severity Index (PASI) score in the foam group decreased by 41% versus 35% in the cream/solution group (P=.17), 3) In scalp psoriasis, the group using the foam had greater improvement in both absolute (P=.03) and percentage (P=.03) terms than the solution group. • When measuring global QOL, foam users had a significantly greater increase in EQ-5D (a quality of life questionnaire) than those using the cream/solution in absolute (P=.05, P=.02) and percentage (P=.04, P=.02) terms (first and second survey components, respectively). Differences in improvement of skin-specific QOL, quantified by the Dermatology Life Quality Index (DLQI) scores between groups, were suggested but not statistically significant. • Patients using foam spent less time applying medication compared

			with previous topical medications (P<.001).
Desonide 0.05% vs. hydrocortisone 1% ointment[15]	n=113	6 month multicenter, randomized, investigator-masked, parallel-group study	In comparing the safety and efficacy of desonide ointment 0.05% to 1% hydrocortisone ointment in children with atopic dermatitis, applied twice daily for 5 weeks, and extended to 6 months in 36 patients: • No differences in safety were observed between hydrocortisone and desonide. • The investigator's global assessment of improvement (improvement in erythema, lichenification, excoriations, oozing, or crusting, pruritus, and induration) significantly favored desonide over hydrocortisone during 3 months of treatment (P<0.05).
Desoximetasone 0.05% gel vs. fluocinonide 0.05% gel[16]	n=125	Double-blind, multicenter study	In evaluating the safety and efficacy of desoximetasone gel 0.05% and fluocinonide gel 0.05% in patients with scalp psoriasis: • Clinical efficacy of desoximetasone appeared equivalent to that of fluocinonide gel 0.05% in treating psoriasis of the scalp, although, desoximetasone appears to be slightly better tolerated.
Flurandrenolide tape vs. diflorasone diacetate[17]	n=30	4 week randomized, bilateral paired-comparison study	In studying the relative efficacy of flurandrenolide tape versus 0.05% diflorasone diacetate ointment in the treatment of plaque psoriasis, when applied once daily (flurandrenolide) for up to 16 hours or twice daily (diflorasone): • Flurandrenolide tape-treated plaques showed consistently greater clearing in terms of erythema, scaling, induration, and treatment success for all plaques as well as the subset of knee and elbow plaques, when compared with the lesions receiving diflorasone diacetate ointment.
0.1% mometasone furoate vs. 0.005% fluticasone propionate[18]	n=40	6 week randomized study	In evaluating the efficacy of 2 newer topical corticosteroids (one-tenth strength diluted 0.1% mometasone furoate ointment and one-tenth strength diluted 0.005% fluticasone propionate ointment) when applied once daily under wet wrap dressings for the treatment of refractory atopic dermatitis in children with moderate to severe disease: • There was significant improvement in the disease severity from baseline during the first 2 weeks (P=0.043), however, additional beneficial effects were limited after week 2. • Wet wraps further improved the disease severity and extent after week 2 (P < 0.05), and were well tolerated. • Both 0.1% mometasone furoate and 0.005% fluticasone propionate ointments are effective in the treatment of atopic dermatitis, and wet wraps are useful in further improving refractory disease in children.

Additional Evidence

Dose Simplification: No peer reviewed studies have evaluated the use of topical anti-inflammatory drugs and adherence.

Stable Therapy: Some of the topical anti-inflammatory agents may be used in acute care situations. No peer reviewed studies were found in the literature evaluating changing from one topical anti-inflammatory agent to another.

Impact on Physician Visits: No peer reviewed data was found in a literature search of Medline/Pubmed and Ovid on topical anti-inflammatory drugs and impact on physician visits.

IX. Conclusions

The topical anti-inflammatory agents offer varying potency groups for the treatment of many dermatologic conditions. Generic alternatives are available in each potency group. There are no significant clinical advantages of one agent over the others in this class, with regards to drug interactions, adverse events, and clinical effectiveness. Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the topical anti-inflammatory agents class and offer no significant advantage over other alternatives in general use.

X. Recommendations

No brand topical corticosteroid is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of the Topical Antipruritics
AHFS 840800
August 11, 2004

I. Overview

The topical antipruritics are used for the short-term (up to 8 days of therapy) treatment of pruritus (itching) associated with dermatitis or lichen simplex chronicus. Their effectiveness appears to be related to H1 and H2 histamine receptor blocking effects. This review encompasses all topical dosage forms and strengths.

Table 1. Products In This Review[2, 3]

Generic Name*	Formulation	Example Brand Name	Supplied
Doxepin	5% cream	Zonalon	30g
Doxepin	5% cream	Prudoxin	45g

*There are no generic formulations available for any of the medications in this class.

II. Treatment Guidelines

Atopic Dermatitis

The mainstay for treatment of atopic dermatitis is topical corticosteroids and immunomodulators (tacrolimus, pimecrolimus). Antipruritics such as doxepin, are mainly geared at alleviating the itching associated with dermatitis.

Pruritus

Pruritus is a common manifestation of dermatologic diseases, including xerotic eczema, atopic dermatitis, and allergic contact dermatitis. When treated effectively, pruritus can prevent scratch-induced complications such as lichen simplex chronicus and impetigo. Causes of systemic pruritus include uremia, cholestasis, polycythemia vera, Hodgkin's lymphoma, hyperthyroidism, and HIV infection.[1] Dermatologic causes of pruritus include allergic contact dermatitis, atopic dermatitis, folliculitis, pediculosis, psoriasis, scabies, sunburn, and xerotic eczema. Table 2 lists nonspecific management options for pruritus.

Table 2. Nonspecific Management of Pruritus[1]

Management Recommendation
• Use of skin lubricants: petrolatum or lubricant cream at bedtime and alcohol-free, hypoallergenic lotions frequently during the day.
• Decrease the frequency and duration of bathing; immediately apply skin lubricant.
• Humidify dry indoor environment, especially in winter.
• Choose clothing that does not irritate the skin.
• Avoid use of vasodilators (e.g. caffeine, alcohol, spices, and hot water).
• Avoid use of provocative topical medications (e.g. corticosteroids), topical anesthetics, and antihistamines due to risk of sensitization of exposed skin and risk of allergic contact dermatitis.
• Prevent complications of scratching by keeping fingernails short and clean.
Topical Treatments • Menthol and camphor (Sarna lotion) • Oatmeal baths • Calamine lotion • Doxepin 5% cream • Burrow's solution (wet dressings) • Unna's boot • Tar emulsion
Systemic Oral Agents • Doxepin (Sinequan) 10-25mg QHS • Hydroxyzine (Atarax) 25-100mg QHS • Nonsedating antihistamines

III. Indications of the Topical Antipruritics

The available doxepin products are indicated for the short-term (up to 8 days) treatment of moderately severe pruritus associated with various forms of eczematous dermatitis, including atopic dermatitis or lichen simplex chronicus.[2, 3]

IV. Pharmacokinetics of the Topical Antipruritics

Absorption
Doxepin is systemically absorbed following topical application. Plasma concentration from the topical formulations range from 0 to 47ng/mL. In contrast, the target plasma concentration following oral therapy is 30 to 150ng/ml. Some patients will reach therapeutic plasma conc. with topical application.[2, 3]

Distribution, Metabolism and Elimination
Absorbed doxepin is metabolized to active desmethyldoxepin. The half-life of both doxepin and desmethyldoxepin are 8 to 24 and 28 to 52 hours respectively. The parent compound and its metabolites are subsequently glucuronidated and excreted in the urine.

V. Drug Interactions

Because clinically important amounts of doxepin may be absorbed percutaneously into systemic circulation following topical application, patients should be cautioned about the risk of adverse events of doxepin, especially drowsiness, and warned that CNS depressant effects of the drug can be exacerbated by alcohol. Table 3 lists documented drug interactions with the topical doxepin products.

Table 3. Doxepin Drug Interactions[4,6]

Drug	Description
Alcohol	May exacerbate potential sedative effects of doxepin cream.
Cimetidine	May increase doxepin concentrations systemically.
MAO Inhibitors	May cause serious side-effects when combined with doxepin systemically.

VI. Adverse Drug Events with the Antipruritics

The risk of systemic toxicity (drowsiness) is increased when doxepin cream is applied to more than 10% of body surface area, and it is particularly important that patients receiving such dosages be cautioned about sedation and other adverse events. Other usual precautions of the tricyclic antidepressants should be considered. The risk of systemic toxicity is increased when the cream is applied to more than 10% of body surface area, and it is particularly important that patients receiving such dosages be cautioned about sedation and other adverse events.[5]

Table 4. Common Adverse Events with Doxepin[2, 3, 4]

Type	Adverse Event
Systemic	• Drowsiness (22%) • Dry Mouth • Headache • Fatigue • Taste Changes • Nausea • Anxiety • Fever (<1%)
Local	• Burning and Stinging at Application site (21%) • Pruritis or eczema exacerbation • Edema • Irritation • Scalling/Cracking

VII. Dosing and Administration

A thin film of cream should be applied to the affected area 4 times daily with at least a 3-4 hour interval between applications. There is no data establishing the safety and efficacy beyond 8 days.[2, 3, 5] Chronic use beyond 8 days may result in higher systemic levels.

Because of potential risk of enhanced percutaneous absorption, doxepin cream should not be used with occlusive dressings and patients should be warned that treated areas of the skin should not be bandaged or otherwise covered or wrapped as to be occlusive.

Special Dosing Considerations

- The safety and efficacy of topical doxepin has not been established in pediatrics, but topical therapy in a limited number of children age 12-18 revealed no evidence of unusual adverse effect.
- Pregnancy category B. There are no adequate and well controlled studies in pregnant women. Use during pregnancy only if clearly needed.

VIII. Effectiveness

A double-blind randomized trial evaluated the effectiveness of topical doxepin in moderate to severe pruritus associated with atopic dermatitis. Topical medications were discontinued at least two days prior to the start of doxepin. The patients completed a severity scale at baseline and at the completion of the study. On opposite ends, the scale was labeled as “no itch” and “worst itch imaginable”. The doxepin treated patients were given 5% doxepin cream with instructions to apply to affected area twice daily on the first day and then four times daily for the remaining days. The other group was given a vehicle cream with the same instructions. The authors concluded that doxepin provided better relief than the vehicle treated patients.[7]

Table 5. Additional Evidence for Doxepin Topical Agents

Study	Sample	Duration	Results
Doxepin vs. capsaisin vs. a combination of both[8]	n=200	4 week randomized, double-blind, placebo-controlled study	To assess the analgesic efficacy of topical administration of doxepin, capsaicin, and a combination of both agents in chronic neuropathic pain: • Overall, pain was significantly reduced by doxepin, capsaicin and by the combination to a similar extent. • The analgesia with doxepin/capsaicin was of more rapid onset. • Capsaicin significantly reduced sensitivity and shooting pain.
Doxepin vs. placebo[9]	n=309	7 day randomized, multicenter, double-blind trial	In order to evaluate the efficacy of doxepin in patients with moderate to severe pruritus, patients were randomized to topical doxepin therapy or placebo. Results showed: • 24 hours after the initiation of therapy, patients treated with doxepin cream experienced significantly greater pruritus relief than did patients given placebo, by all efficacy parameters ($p<0.002$). • 60% of the doxepin treated patients experienced pruritus relief within 24 hours, and the response rate increased to 84% by conclusion of the study.

Additional Evidence

Dose Simplification: Not Applicable.

Stable Therapy: Not Applicable.

Impact on Physician Visits: No peer reviewed data was found in a literature search of Medline/Pubmed and Ovid relating to use of topical doxepin and impact on physician services.

IX. Conclusions

Topical doxepin provides an additional option to treat moderate pruritus. It possesses less unwanted side effects when compared with oral agents used to treat the same condition. Treatment should be limited to 8 days in order to avoid adverse drug reactions associated with systemic absorption. There are no differences in the doxepin topical agents in this class. Therefore, all brands within the class reviewed are comparable to each other and to the generics and OTC products and offer no significant clinical advantage over other alternatives in general use.

X. Recommendations

No brand topical antipruritic is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of the Astringents
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I. Overview[1-4]

Astringents are products that cause dehydration, tightening of the skin, shrinking of tissues and contraction of skin pores. Prescription drugs that are astringents are used in the treatment of hyperhidrosis (excessive sweating) and non-legend drugs are sometimes used to aid wound healing. Aluminum Chloride is the active chemical ingredient in the drugs used to treat hyperhidrosis, and Peruvian Balsam (Balsam of Peru) and Castor Oil are the chemical ingredients found in over-the-counter products used to promote wound healing. The focus of this review will be on the legend products used to treat hyperhidrosis. The product, Amberderm, is an over-the- counter drug with limited scientific information.

Hyperhidrosis may be focal or generalized. Focal hyperhidrosis usually affects the axillae, palms, soles of the feet, face, and, rarely, other areas. It can be extremely disabling in both private and professional life. Focal hyperhidrosis affects up to 0.5% of the population and usually appears during the second or third decade of life. For research purposes, hyperhidrosis is defined quantitatively as the production of more than 100mg of sweat in 1 axilla over 5 minutes.

Focal hyperhidrosis is most often essential, or idiopathic, and results from a neurogenic overactivity of the sweat glands in the affected area. The palms and/or soles of the feet (palmoplantar hyperhidrosis) are affected in about 60% of patients, and the axillae are affected in 30% to 40%. Facial sweating is less frequent and affects up to 10% of patients with idiopathic hyperhidrosis. Facial hyperhidrosis should be distinguished from gustatory sweating, which is a secondary form of hyperhidrosis that occurs on the cheek in response to salivation or anticipation of food. The cause of essential focal hyperhidrosis is unknown at present. The sweat glands and their innervations do not show any histologic abnormalities. A dysfunction of the central sympathetic nervous system, possibly of hypothalamic nuclei, or prefrontal areas or their connections is suspected. Generalized hyperhidrosis, in which sweating occurs over the whole body, has many causes, including diabetes, chronic infectious diseases, and malignancy.

Acetylcholine is the major neurotransmitter, making eccrine gland sympathetic innervation unique; noradrenaline is generally the neurotransmitter in sympathetic nerves. Other mediators have been localized in the periglandular nerves, such as adenosine triphosphate, natriuretic peptide, calcitonin gene-related peptide, galanin, catecholamines, and vasoactive intestinal peptide. The significance of these substances is not fully understood.

This review encompasses all topical dosage forms and strengths. Table 1 lists the products in this review.

Table 1. Products In This Review

Generic Name	Formulation	Example Brand Name
Aluminum Chloride	20% Solution	Drysol*
Aluminum Chloride	20% Solution	Hypercare*
Aluminum Chloride	6.5% Solution	Xerac AC 6.5%
Aluminum Chloride	20% Solution	Aluminum Chloride Solution (generic) 20%
Peruvian Balsam and Castor Oil	Aerosol	AmberDerm*

*Generic Available

II. Treatment Guidelines[5-7]

Treatment for hyperhidrosis ranges from topical treatment with antiperspirants to surgical procedures. Generally accepted treatment steps are as follows:

First Line – Topical products containing aluminum chloride
Second Line – Iontophoresis or Botulinum Toxin Type A
Third Line – Endoscopic surgery to clip the responsible nerves

Several chemicals can be used to reduce excessive sweating. Today, aluminum is the metal salt most commonly used. Patients with hyperhidrosis do not find commercially available over-the-counter antiperspirants or deodorants to be effective, although many have difficulty giving them up even when relief has been obtained with other measures.

Aluminum chloride in higher concentrations than that found in over-the-counter products is effective for many patients with hyperhidrosis. After improvement is noticed, the patient should gradually decrease the frequency of application to minimize side effects such as dryness, irritation, and fissures.

Drysol and Hypercare are prescription-only solutions of 20% aluminum chloride in anhydrous ethyl alcohol. Xerac AC is a solution of aluminum chloride 6.25% in anhydrous ethyl alcohol with a Dab-O-Matic head for application. It, too, requires a physician's prescription, but is generally not as effective as the 20% solution for most hyperhidrosis patients.

Iontophoresis, the topical introduction of ionized medications into the skin using direct current, can be quite effective for most patients with hyperhidrosis. Iontophoresis is generally used for palmar/plantar hyperhidrosis. Levit has shown that simple galvanic devices relieved symptoms in 85% of affected patients.[7] A small direct electronic current (~15mA) is passed through the skin. Tap water is usually employed, but sometimes anticholinergic agents are added. Iontophoresis may work by "plugging" the sweat ducts or by inducing an electrical change in the sweat gland that disrupts secretion. The greatest drawback of iontophoresis for many patients is the time required to perform the treatments.

Botulinum toxin type A is a minimally invasive, effective, safe treatment for axillary hyperhidrosis, which due to its temporary effect of about 7 months has to be performed repeatedly. ETS (endoscopic thoracic surgery) has proved a highly effective treatment option for axillary hyperhidrosis, but there is a high risk of compensatory sweating, and there are rare perioperative complications.

III. Comparative Indications for the Astringents[8,9]

Table 2. FDA-Approved Indications for the Astringent Products

Generic Name	Formulation	Indication
Aluminum Chloride	20% Solution (Drysol)	Hyperhidrosis
Aluminum Chloride	20% Solution (Hypercare)	Hyperhidrosis
Aluminum Chloride	6.5% Solution	Hyperhidrosis
Aluminum Chloride	20% Solution (generic)	Hyperhidrosis
Peruvian Balsam and Castor Oil	Aerosol	Wound Healing

Aluminum chloride is the main ingredient in the products being compared. The single approved indication for the astringents that contain aluminum chloride is for treatment of hyperhidrosis.

IV. Comparative Pharmacology and Pharmacokinetic Parameters of Aluminum Chloride Astringents[9,10]

Aluminum chloride is an ethanolic solution, that, when applied topically, penetrates the acrosyringium of the sweat glands and forms a plug, thereby reducing the amount of sweat. The differences between the products relates to strength of the active ingredient and the percent of alcohol in the individual products.

Table 3. Differing Content of the Aluminum Chloride Products

Product Brand Name	Aluminum Chloride Strength	Alcohol Content
Drysol	20%	93%
Hypercare	20%	93%
Xerac AC	6.5%	96%
Aluminum Chloride Solution (generic)	20%	93%

V. Comparative Drug Interactions for the Astringents[8,9]

There are no drug interactions noted for these topical products.

VI. Comparative Adverse Effects[8,9]

All products in this category have similar adverse effects. Transient stinging or itching may occur, and if intense, the product can be removed with soap and water. A rash may develop.

VII. Dosage and Administration[9,11]

Topical solution should only be applied to absolutely dry skin. Dry skin can be achieved by blow drying with a hair dryer on a warm setting for a few minutes. Medication should be kept on the skin for 6-8 hours, during which sweating does not occur. For best results the topical solution should be applied only before bedtime, since the sweat glands remain inactive during the tranquility of sleep. Do not apply to broken, irritated or recently shaved skin. If applying to the palms or the feet, wrap with saran wrap and then cover with a glove or sock. If applying to the scalp, wear a plastic shower cap during sleep. If applying to underarms wear a T-shirt. The next morning, remove coverings (discard saran wrap) and wash the treated area thoroughly with a mild soap or a mild shampoo to remove the residual aluminum chloride. Towel dry the skin or scalp. Do not apply other deodorants or antiperspirants while using the aluminum chloride products. Repeat applications for 2 or 3 nights, until the desired effect is achieved. After that, an application once or twice a week should maintain needed controlled protection from hyperhidrosis.

Special Dosing Considerations
None

VIII. Effectiveness

Control of hyperhidrosis with aluminum chloride depends on the severity of hyperhidrosis. For very mild cases of hyperhidrosis, a product that contains 6.5% aluminum chloride may be effective. For moderate to severe cases a product that contains 20% aluminum chloride will need to be used. Higher concentration of aluminum chloride may be necessary to produce adequate results. Laboratories can supply the physician with suitable preparations. It is not recommended to use concentrations higher than 35% due to the high incidence of irritation and fissuring. In palmar hyperhidrosis, these reactions can sometimes be managed with topical over-the-counter lotions and hand creams. The use of aluminum chloride products to control hyperhidrosis is usually the first line of therapy and probably the least expensive, but severe cases may not respond.

Additional Evidence

Dose Simplification: Not Applicable.

Stable Therapy: No peer reviewed studies were found in a literature search of Medline/Pubmed and Ovid addressing use of aluminum chloride for hyperhidrosis and changing to alternative therapies.

Impact on Physician Visits: No peer reviewed studies were found in a literature search of Medline/Pubmed and Ovid on the impact of aluminum chloride products on physician visits.

IX. Conclusions

Aluminum chloride products should be first line treatment for hyperhidrosis. Iontophoresis and Botulinum toxin type A are considered second line treatment and ETS is reserved as third line treatment for the severe nonresponders.

There are no head to head, brand to generic, studies of the aluminum chloride products. At the current time there are no generic products that contain 6.5% aluminum chloride and most likely only the mildest cases will respond to the 6.5% concentration.

Therefore, all brand products within the class reviewed are comparable to each other and to the generics and OTC products in the class and offer no significant clinical advantage over other alternatives in general use.

X. Recommendations

No brand astringent is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of the Keratolytics
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I. Overview

Podophyllum Resin
Podophyllum resin (at a strength of 25%) is used for the removal of soft genital (venereal) warts (condylomata acuminata) and other papillomas; for multiple superficial epitheliomatosis and keratoses.[1]

Condylomata acuminata is a sexually transmitted lesion that has become a major health care problem in the US. It is caused by the human papillomavirus (HPV) and is linked to cancer in both men and women. This condition can be treated medically and surgically, alone or in combination.[2] Even though alternative treatments are available, the CDC still recommends podophyllum resin as an alternative regimen to cryotherapy for the treatment of external genital/perianal warts, vaginal warts and urethral meatus warts.[3]

Podophyllum resin is the powdered mixture of resins removed from the May apple or Mandrake (*Podophyllum peltatum* Linne'), a perennial plant of the northern and middle US. Podophyllum is a cytotoxic agent that has been used topically in the treatment of genital warts. It arrests mitosis in metaphase, an effect it shares with other cytotoxic agents such as the vinca alkaloids. The active agent is podophyllotoxin, whose concentration varies with the type of podophyllum resin used; American podophyllum typically has a reduced level of podophyllotoxin and normally contains one-fourth the amount of the Indian source.[1]

Urea (Carbamide)
In normal skin, the stratum corneum serves as a protective barrier against excessive evaporative water loss and environmental insults. The extensibility of the stratum corneum depends on its water content and environmental temperature. When the stratum corneum contains more than 10% water, it remains soft and pliable. However, when the water content drops below 10%, the stratum corneum becomes less flexible and rough. It may exhibit scaling and cracking and the underlying skin may become irritated.
These changes may produce a condition of excessive dryness of the skin, known clinically as xerosis.

Several studies have shown that emollients and humectants are essential in the management of dry skin conditions, like atopic dermatitis, ichthyosis vulgaris, psoriasis and aging. Preparations containing **urea** were found to be effective in the treatment of ichthyosis vulgaris and foot xerosis.

Effectiveness of different products can be assessed by clinical criteria. The choice of the " ideal " moisturizer depends on the dermatosis (clinical appearance and phase such as acute, chronic, active or maintenance), the product (mechanisms of hydration are different depending on the molecule: occlusion, humectation, active hydration), and experience of the practitioner and patient preference.[4]

Since urea is a tissue softener, it can also be used for the chemical avulsion of nails. It is not effective for the avulsion of normal nails.[5]

The medications listed in Table 1 are included in this review. This review encompasses all topical dosage forms and strengths.

Table 1. Keratolytic Drugs in This Review[1]

Generic Name	Formulation	Example Brand Name (s)
Podophyllum resin (Podophyllin)	Liquid 25%*	Podocon-25
Podophyllum resin (Podophyllin)	Liquid 25%*	Podofin
Urea	Cream 40%*	Carmol 40, Vanamide, Gordon's Urea
Urea	Scalp Lotion 10%	Carmol
Urea	Lotion 40%*	Urea, RE Urea 40
Urea	Gel 40%*	Carmol 40, RE 40, Keratol 40
Urea / hydrocortisone	Cream 10%/1%*	Carmol HC, U-Cort

*Generic Available

Note: Urea 10% and 20% creams are available over-the-counter and are not covered in this review.

II. Current Treatment Guidelines

Veneral Warts (HPV)

Several types of medical therapy are available for treatment of genital warts. They include podophyllum, podophyllotoxin, trichloroacetic acid, imiquimod, fluorouracil, thiotepa, and immunotherapy with intralesional interferons. Surgical treatment is also an option and has been shown to be superior to treatment with podophyllin in randomized trials. However, the Centers for Disease Control (CDC) and Prevention endorses podophyllin, TCA, podophyllotoxin, imiquimod, intralesional interferons, cryotherapy, electrosurgery, laser surgery and surgical excision for the management of genital warts, although the order in which these different modalities are used is left to the discretion of the physician.[2] The following is a summary of the CDC's 2002 Recommendation for the treatment of genital warts.

CDC-Treatment Guidelines for the Treatment of Human Papillomavirus[6]

- More than 30 types of human papillomavirus (HPV) can infect the genital tract. Most HPV infections are asymptomatic, unrecognized, or subclinical. Visible genital warts usually are caused by HPV types 6 or 11. Other types of HPV (16, 18, 31, 33, and 35) have been strongly associated with cervical neoplasia. Patients infected with visible genital warts can be infected simultaneously with multiple HPV types.
- Diagnosis can be confirmed by biopsy, although biopsy is only necessary when diagnosis is uncertain or if lesions do not respond to standard treatments.
- The primary goal of treatment is the removal of symptomatic warts. In most patients, treatment can induce wart-free periods. Existing data indicate that currently available therapies for genital warts may reduce, but probably do not eradicate infectivity. Whether the reduction in viral DNA that results from current treatment regimens impacts future transmission remains unclear. No evidence indicated that either the presence of genital warts or their treatment is associated with the development of cervical cancer.
- Treatment of genital warts should be guided by preference of the patient and the experience of the health-care provider. No definitive evidence suggests that any of the available treatments is superior to the others, and no single treatment is ideal for all patients or all warts.
- Factors that may influence the selection of treatment include wart size, wart number, anatomic site of wart, wart morphology, patient preference, convenience, and adverse effects.
- The treatment should be changed if the patient has not improved substantially after 3 provider-administered treatments or if warts have not completely cleared in six treatments. Both provider administered and patient administered treatments are available.
- Treatment recommendations for external genital warts:

  Patient Applied: Podofilox (Condylox) 0.5% solution or gel
  Imiquimod 5% cream

  Provider Applied: Cryotherapy with liquid nitrogen or cryoprobe
  Podophyllin resin 10-25%
  Trichloroacetic acid (TCA)or bichloroacetic acid

  Alternative regimens for external genital warts: Intralesional interferon
  Laser surgery
- Podophyllum resin is also recommended in regimens for urethral meatus warts.

Skin Conditions

Preparations containing urea were found to be effective in the treatment of ichthyosis vulgaris and foot xerosis, and are used by practitioners in the treatment of other dry skin conditions.[4] Urea is also effectively used as an enzymatic debrider to promote healing in certain conditions.[7, 8, 9] Urea products enzymatically debride and promotes healing of surface lesions, particularly where healing is retarded by local infection, necrotic tissue, fibrinous or purulent debris, or eschar. Treatment with urea for the avulsion of dystrophic nails can be done surgically, but in patients where surgery is either contraindicated or undesirable, urea 40% is the preferred option.

III. Indications of the Keratolytics

Podophyllum resin can be used for the treatment of external genital and perianal exophytic warts caused by HPV. The drug can also be used in the treatment of urethral HPV warts, but is not recommended for the treatment of vaginal, cervical, intra-anal, or oral HPV warts.[10]

Table 2. Indications for the Topical Keratolytic Agents[1, 7, 8, 9, 10]

Agent	Indication
Podophyllum resin 25% (Podocon and Podofin)*	Removal of soft genital (venereal) warts (condylomata acuminata) and other papillomas; for multiple superficial epitheliomatosis and keratoses.
Urea	Promote hydration, remove excess keratin in dry skin and hyperkeratotic conditions. Urea 40%: Treatment of nail destruction and dissolution. It removes dystrophic and potentially disabling nails without local anesthesia and surgery.

*The CDC recommends podophyllum resin as an alternative regimen to cryotherapy for the treatment of external genital/perianal warts, vaginal warts and urethral meatus warts.

IV. Drug Interactions

There are no drug interactions noted with topical podophyllum resin or with the urea agents.

V. Adverse Effects

Although not likely, topical podophyllum can become absorbed systemically.[11] The following side effects listed in Table 3 indicate absorption of the drug. Local adverse effects can also occur and they include burning, redness, skin rash, itching or irritations of application area.

Table 3. Adverse Effects of Systemically Absorbed Podophyllum[11]

Occurrence	Adverse Effect
Early Symptoms	Abdominal or stomach pain; clumsiness; confusion; decreased or loss of reflexes; diarrhea; excitement; irritability; hallucinations; muscle weakness; nausea or vomiting; sore throat and fever; unusual bleeding or bruising.
Late Symptoms	Constipation; convulsions; difficult or painful urination; difficulty breathing; dizziness; drowsiness; tachycardia; numbness; tingling; pain or weakness in hands or feet.

Transient stinging, burning, itching and irritation may occur with all of the topical urea products.

VI. Dosing and Administration of the Topical Keratolytics

Table 4. Dosing and Administration for Podophyllum and Urea

Agent	Dose Instructions
Podophyllum resin 25%	Not to be applied by the patient. For physician use only. Directions: Thoroughly cleanse affected area. Use applicator to apply sparingly to lesion. Avoid contact with healthy tissue. Allow to dry thoroughly. Treat only intact (non-bleeding) lesions. As podophyllum is a powerful caustic and severe irritant, it is recommended the first application be left in contact for only a short time (30 to 40 minutes) to determine patient's sensitivity. To avoid systemic absorption, use the minimum time of contact necessary to produce the desired result (1 to 4 hours, depending on condition of lesion and of patient), with the physician developing their own experience and technique. Do not treat large areas or numerous warts at on time. After treatment time has elapsed, remove dried podophyllum resin thoroughly with alcohol or soap and water. [1, 10, 11]
Urea	For skin conditions-Apply 2 to 4 times daily to affected area or as directed. Rub in completely. For nail avulsion-Cover surrounding surfaces. Generously apply directly to the diseased nail surface and cover with plastic film, wrap and anchor with adhesive tape. Cover with a "finger" cut from plastic or vinyl glove and anchor with more tape. Keep completely dry. Remove treated nails in 3, 7 or 14 days. Nail bed usually hardens in 12 to 36 hours when left open to the air. [1, 7, 8, 9]

Pregnancy:
There have been reports of complications associated with the topical use of podophyllum on condylomas of pregnant patients including birth defects, fetal death and stillbirth. Use is not recommended for pregnant patients or patients who plan to become pregnant. [1]

Lactation:
It is not known whether podophyllum is excreted in breast milk following topical application. Do not use on nursing patients. [1]

Special Dosing Considerations

- Podophyllum resin is contraindicated in patients with diabetes; patients using steroids or with poor blood circulation; use on bleeding warts, moles, birthmarks or unusual warts with hair growing from them; pregnancy, and lactation. The drug is a pregnancy category C.
- The safety and efficacy of podophyllum in pediatric patients has not been established.
- Urea products are considered pregnancy category C.

VII. Effectiveness

Podophyllin resin is effective for the removal of genital warts and is recommended by the CDC. Some studies indicate podophyllin is not as effective as other options available for the treatment of genital warts. Although clinical data is limited, Table 5 illustrates clinical comparative data for podophyllin versus other treatment choices.

Table 5. Additional Clinical Efficacy Studies

Study	Sample	Duration	Results
Podophyllin vs. cryotherapy vs. electrodesiccation[12]	n=450	Randomized trial	Patients being seen in a public sexually transmitted diseases clinic were randomized to podophyllin, cryotherapy or electrodesiccation. Results indicated: • Complete clearance of warts was observed in 41%, 79%, and 94% of patients who received up to six weekly treatments or podophyllin, cryotherapy, and electrodesiccation. • Relapses occurred in 25% of all patients, yielding 3 month clearance rates of 17%, 55%, and 71% for podophyllin, cryotherapy, and electrodesiccation. • Wart volume and duration did not influence treatment outcome. • Response was greater in women than men, and did not differ by treatment modality. • Electrodesiccation and cryotherapy were more effective than podophyllin for the treatment of external genital warts, but not of the three treatments were highly successful.
Interferon alpha 2b plus podophyllin vs. podophyllin alone[13]	n=97	3-week Randomized trial	In evaluating the value of combining interferon with standard local therapy in the treatment of HPV: • Maximal responses occurred within 2 weeks of therapy, and overall, there was complete clearance of treated warts in 67% of patients receiving the combination versus 42% of patients who received the podophyllin monotherapy. • Of patients with complete clearance, 67% of the combination group versus 65% of the podophyllin monotherapy group experienced recurrences.
Interferon alpha-2a vs. podophyllin[14]	n=154	Six week randomized open study	In comparing the response to treatment and recurrence rate of genital warts using SQ injection of interferon alpha 2a for 4 weeks of podophyllin resin 25% for up to 6 weeks: • A complete response was achieved at 3 months in 15 of 64 (23%) of patients in the interferon group and 31 of 69 (45%) in the podophyllin treated group (P=0.003). • At nine months, 10 of 13 patients in the interferon group and 22 of 30 patients in the podophyllin group remained completely clear of lesions.
Imiquimod vs. podophyllotoxin[15]	-	A model based comparison	In evaluating the efficacy of treatment of external anogenital warts with imiquimod and podophyllotoxin, followed by laser treatment in patients who relapsed: • Imiquimod provided a clearance rate of 49.5% at 16 weeks, compared to a rate of 28.3% with podophyllotoxin at 4 weeks. • The relapse rate was lowest with imiquimod (13.3%) versus that of podophyllotoxin (30.9%).

Additional Evidence

Dose Simplification: Not Applicable.

Stable Therapy: Not Applicable.

Impact on Physician Visits: Data suggests that per capita condylomata visits per physician are highest for obstetrician / gynecologists, dermatologists, and urologists, a fact that may imply these specialists have expertise in treating these patients.[16] On average, individual episodes of care for genital warts involves 3.1 physician visits.[17] In an analysis to determine which treatment modalities for condylomata acuminate are associated with the lowest direct and indirect utilization of medical services, the available treatments were ranked by complete clearance, from lowest to highest utilization of resources.[18] Surgical excision was the treatment modality with the lowest utilization of medical resources. Other treatments associated with lower medical utilization were loop electrosurgical excision, electrodesiccation, carbon dioxide laser, podofilox, and pulsed-dye laser. Treatments associated with higher medical utilization were cryotherapy, trichloroacetic acid, imiquimod, podophyllum resin, and interferon alfa-2b.
Surgical therapies (cryotherapy, electrotherapy, laser surgery, and surgical excision) are generally equivalent in terms of wart clearance rates, but are associated with high rates of wart recurrence.[19] Trichloroacetic acid's efficacy is not well documented and has a tendency to have unpleasant side-effects. Patient applied therapies are more acceptable treatments for patients and sometimes providers. The wart clearance rate for imiquimod and podophyllotoxin are similar, although imiquimod is associated with lower recurrence rates. While no studies specifically looked at the direct impact of treatments for condylomata on physician visits, recurrence rates may correlate to the number of times a patient must follow-up with his/her provider. The severity and location of disease may also influence treatment.

VIII. Conclusions

There is no single treatment that is advantageous over others in the treatment of genital warts caused by HPV. All recommended treatment options should be considered by the patient and provider, based on the specific lesions being treated. Generic products are available for most of the products in this class and there are no clinical advantages of using the brands versus the generics.

The urea products, although not commonly used, are also available generically. These products are effective for certain skin conditions.

All brand products in the keratolytic class are comparable to each other (the urea products and the podophyllin products) and to the generics and OTC products in this class and offer no significant clinical advantage over other alternatives in general use.

IX. Recommendations

No brand keratolytic is recommended for preferred status.

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Pharmacotherapy Review of the Keratoplastic Agents
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I. Overview

Topical coal tar and anthralin preparations are classified as keratoplastics. Topical coal tar has a variety of uses including treatment of psoriasis, seborrheic dermatitis, and dandruff. Tar shampoos are often effective for scalp psoriasis. The use of coal tar was first described by Goeckerman in 1925, when it was combined with ultraviolet light for the treatment of psoriasis. Medicinal use of coal tar likely stemmed from studies of the drug and its carcinogenic properties. Researchers studied coal tar in these trials by applying it to the skin of mice, subsequently noticing improvements in the skin conditions of mice with psoriasis. It is thought to suppress epidermal DNA synthesis.[1] Anthralin, also known as dithralin, is a topical product also used to treat psoriasis. It has been available since 1916, but traditionally has not been used a first line agent because of its staining and irritant properties. This review encompasses all dosage forms and strengths.

Table 1. Coal Tar and Anthralin Agents In This Review

Generic Name	Dosage Formulation	Example Brand Name (s)	Rx vs. OTC
Coal Tar	Shampoo 0.5%*, 1%*, 1.2%, 2%*, 4.5%, 5%, 6.65%*, 15%* Liquid 2.5%, 7.5% Oil 2% Ointment 1%, 10% Cream 2%* Lotion 25% Gel 5% Soap 2.5%	Doak Tar, Doak Tar Lotion, Doak Tar Oil, Neutrogena T/Gel Original, Balnetar, Medotar, PsoriGel, Polytar, Denorex, Denorex Extra Strength, DHS Tar, DHS Tar Gel, Oxipor VHC, Doctar, Estar, Fototar, G-Tar, Ionil T, Ionil T Plus, Theraplex T, Therapeutic Shampoo	OTC
Anthralin	Cream 0.25%, 1%* Ointment 0.25%, 0.5%, 1%	Anthra-Derm, Drithocreme, Anthralin	Rx

*Generic Available

II. Current Treatment Guidelines

While topical corticosteroids are the mainstay of treatment for psoriasis, coal tar and anthralin are effective treatment options.[1,2] Coal tar is most effective when it is used in combination with other agents, such as corticosteroids, and especially ultraviolet B light. Coal tar shampoo can be used in combination with a corticosteroid scalp solution for the treatment of psoriasis on the scalp.[1] If good control of psoriasis is not achieved with first line therapy (e.g. topical corticosteroids, alone or in combination with calcipotriene or coal tar), addition of anthralin therapy may be considered.

Figure 1 and Table 1 summarize the recommend therapies for localized and generalized psoriasis, respectively.

Figure 1. Algorithm for the treatment of localized psoriasis. Treatment of localized psoriasis is initiated using topical corticosteroids, alone or in combination with coal tar or calcipotriene. Patients with resistant lesions may benefit from the addition of anthralin or tazarotene.[1,2]

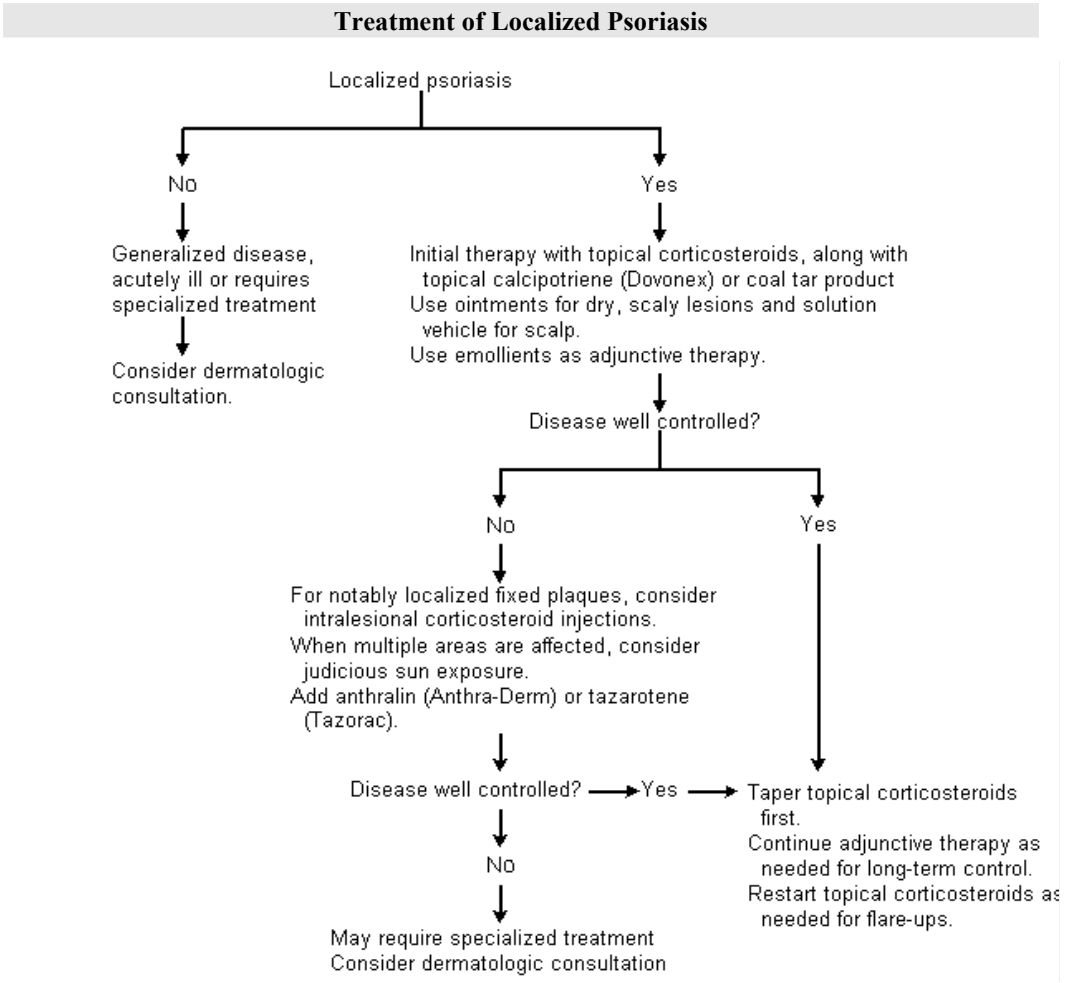

Table 2. Therapy for Generalized Psoriasis[1,2]

Therapy	Characteristics that guide the choice of therapy
Ultraviolet B (UVB) light	Used for many years, highly effective. May cause acute phototoxicity. Little to no long-term side effects. UVB can be used at home for maintenance therapy.
Psoralen plus ultraviolet A (PUVA)	Highly effective; can be used as maintenance therapy. High risk of acute phototoxicity. Long-term risks include high risk of cutaneous malignancy.
Retinoids (acitretin [Soriatane])	Moderately effective; best for pustular psoriasis. Potent teratogen; use in women of childbearing potential should be avoided. Causes dryness of skin. May cause elevation of triglycerides. Hyperostosis with long-term use.
Methotrexate (Rheumatrex)	Highly effective and can be used on a long-term basis. Should not be used in noncompliant patients or when there is preexisting hepatic disease. Can cause acute or chronic hepatotoxicity, and acute neutropenia and pancytopenia.
Cyclosporine (Sandimmune)	Highly effective. Careful monitoring required. The long-term risk of renal toxicity, which may not be detectable by blood tests, limits long-term use.

Frequently used or well-studied combination therapies
- UVB plus topical calcipotriene (Dovonex)
- **UVB plus topical coal tar**
- PUVA plus topical calcipotriene
- PUVA plus retinoids
- Acitretin plus topical calcipotriene
- Cyclosporine plus topical calcipotriene

Infrequently used or less well-studied therapies
- UVB plus methotrexate
- PUVA plus methotrexate

III. Indications

Coal tar – For treatment of scalp psoriasis or as adjunct therapy of psoriasis, seborrheic dermatitis, dandruff, cradle-cap, and other oily, itchy conditions of the body and scalp.

Anthralin – for the treatment of quiescent or chronic psoriasis.

IV. Pharmacokinetics

Pharmacokinetic data for the products in this class is not available in multiple pharmacy reference manuals. Through topical application, it is thought that coal tar abstracts oxygen from the skin, thereby inhibiting cell reproduction and causing a decrease in the size and number of cells in the stratum germinativum and stratum corneum. Therefore, the primary effects are local and it is likely that little drug is absorbed.

V. Drug Interactions

Although no drug interactions have been reported to date, it is recommended that coal tar preparations not be used concomitantly with drugs having phototoxic and/or photoactivating potential.

VI. Adverse Drug Events

Coal tar is messy, malodorous and can stain clothing.[1] Minor dermatologic side effects include folliculitis, rash or burning sensation may occur with therapy. Photosensitivity and skin discoloration may occur. High concentrations of some chemicals in coal tar may cause cancer. However, concentrations of 0.5% to 5% appear to be safe.[3]

Anthralin has a tendency to stain any surface, including the skin, clothing and bathtub. Patients should be warned that normal skin surrounding the psoriatic lesion may become irritated if it comes in contact with anthralin. Very few instances of contact allergic reactions to anthralin have been reported. However, transient primary irritation of normal skin or uninvolved skin surrounding the treated lesions is more frequently seen and may occasionally be severe. Application must be restricted to the psoriatic lesions.[3]

VII. Dosing and Administration

Table 3. Coal Tar Dosing and Administration

Coal Tar
Shampoo - Rub shampoo liberally into wet hair and scalp. Leave on for several minutes. Rinse thoroughly. Repeat and rinse. Depending on product, shampoo from once daily to at least twice a week or as directed by a physician. For severe scalp problems, use daily.
Bath preparations - Add to bath water. Soak 10 to 20 minutes and then pat dry.
Other (lotions, creams, solutions) - Refer to specific product labeling. Depending on product, application is from 1 to 4 times/day.

Table 4. Anthralin Dosing and Administration

Anthralin
Application - Once a day. Initiate treatment using the lowest strength for the first week.
Skin application – ▪ Apply sparingly only to the psoriatic lesions and rub gently and carefully into the skin until absorbed. ▪ Avoid applying an excessive quantity, which may cause unnecessary soiling and staining of the clothing or bed linen. ▪ After each treatment, take a bath or shower to remove any surplus (cream may have become red/brown in color). ▪ The margins of the lesions may gradually become stained purple/brown as treatment progresses, but this will disappear after treatment cessation.
Scalp application– ▪ Comb the hair to remove scalar debris and, after suitably parting, rub the cream well into the lesions, taking care to prevent the cream from spreading onto the forehead. ▪ Keep away from the eyes. Take care to avoid application to uninvolved scalp margins. Remove any unintended residue, which may be deposited behind the ears. ▪ After each treatment, wash the hair and scalp to remove any surplus (cream may have become red/brown in color).

The optimal period of contact with anthralin varies according to the strength used and the patient's response to treatment. Continue treatment until the skin is entirely clear (e.g. when there is nothing to feel with fingers and the texture is normal).[3]

Short-contact regimens have been used preferably for stable plaque-type psoriasis. Initial contact time is 0.1% to 2% for 15 to 20 minutes, followed by thorough removal of the anthralin with an appropriate solvent (soap or petrolatum) and application of an emollient. Short-contact therapy plus other treatments (e.g. ultraviolet light, retinoids, topical steroids, psoralens plus UV light) may improve the response.[3]

Special Dosing Considerations

- Coal tar: High concentrations of some chemicals in coal tar may cause cancer. However, concentrations of 0.5% to 5% appear to be safe. Safety and efficacy of coal tar preparations in children have not been established. It is not known whether coal tar preparations can cause fetal harm when used topically by pregnant women.
- Anthralin: Pregnancy category C. Safety and efficacy of anthralin use in children has not been established. Although no renal or hepatic abnormalities have occurred with topical application, caution should be used in patients with renal disease and in those having extensive and prolonged applications. Periodic urine tests for albuminuria should be performed.

VIII. Effectiveness

Coal Tar

Two recent studies compared a 1% preparation of coal tar in a fatty acid base to calcipotriol and to a conventional 5% coal tar preparation. In the first study by Tzaneva, et al, the therapeutic efficacy, safety and cosmetic acceptability of the 1% coal tar preparation was compared with calcipotriol cream. Forty patients with chronic plaque type psoriasis were included in this randomized, observer-blind, intrapatient comparison trial. In each patient, two comparable target plaques were treated twice daily with 1% coal tar preparation or calcipotriol cream[4]:

- At the onset of therapy and at weeks 2, 4, 6 and 8, the response to treatment was determined by the psoriasis severity index (PSI) that assesses the degree of erythema, infiltration and scaling of the psoriatic lesions on a five-point scale. In addition, all treatment-related side-effects were recorded and cosmetic acceptability of both treatments was rated every second week by the patients.
- After complete or near complete clearing the patients were followed up until relapse or for a maximum period of 18 months. Thirty-eight patients completed the study.
- At termination of the trial the mean ± SD baseline PSI score of 9.2 ± 1.5 was reduced to 3.0 ± 2.9 by 1% coal tar preparation and to 2.8 ± 2.7 by calcipotriol.
- The mean PSI reduction between baseline and final assessment did not differ significantly between 1% coal tar preparation and calcipotriol.
- The mean intraindividual difference in reduction of PSI score between 1% coal tar preparation and calcipotriol was 0.1 score points (95% confidence interval) -0.84 to + .0.63.
- No difference between either preparation was observed with regard to time until relapse. Itching was caused by 1% coal tar preparation in four patients and by calcipotriol in one patient.
- Unpleasant odor or staining of the 1% coal tar preparation was reported by six patients, whereas one patient complained about the smell of the calcipotriol cream.
- Coal tar 1% preparation was found to be comparably as effective as calcipotriol in treating psoriasis.
- Tolerability and cosmetic acceptability was better for calcipotriol.

In the second study Goodfield, et al[5] found the efficacy and tolerability of 1% prepared coal tar lotion (fatty acid based lotion) was compared to 5% coal tar extract in patients with mild to moderate plaque psoriasis. This was a double-blind, randomized controlled study lasting 12 weeks[5]:

- Three hundred twenty four of the 338 randomized patients were randomized and 228 patients completed the full course of therapy.
- The clinical measures used were: 1) Total Sign Score (TSS), the sum of 5-point rating scores for erythema, induration and scaling averaged for the two target plaques (range 0-12), 2) the Psoriasis Area and Severity Index (PASI), and 3) patient and investigator 7-point global assessments of improvement at 12 weeks.
- Patients were assessed at 0, 4, 8 and 12 weeks during the treatment period or at the point of withdrawal. Spontaneously reported and observed adverse events were noted.

- Three hundred and twenty four of 338 randomized patients were available for evaluation: 158 patients received 1% coal tar lotion and 166 patients received conventional coal tar.
- Both groups showed decreases from baseline to end of treatment in mean TSS (decrease of 2.4 points from 5.6 to 3.2 with 1% coal tar lotion and 1.8 points from 5.5 to 3.7 with conventional coal tar), and mean PASI (decrease of 2.4 points with 1% coal tar lotion and 1.5 points with conventional coal tar).
- Two hundred and twenty eight patients completed the full course of treatment. There was a statistically significant treatment difference in the percentage change in mean TSS at week 12, in favor of 1% coal tar lotion (-10.6%, 95% CI -20.6% to -0.5%, p=0.04).
- There was also a difference between treatments in the change in mean PASI in favor of 1% coal tar that was of borderline statistical significance (-11.7%, 95% CI -23.8% to 0.4%, p=0.06).
- Investigator global assessments also favored 1% coal tar lotion (38% vs. 27% of patients showed clearance or marked improvement).
- Coal tar 1% was found to be more effective than the 5% lotion.
- The 1% coal tar lotion had a similar safety profile to 5% conventional coal tar lotion with the majority of treatment-related events being mild to moderate in severity.

Anthralin

Dutz and Lui performed an open, controlled, bilateral half-body comparison study on 18 patients that evaluated the efficacy of calcipotriol/tar/UVB vs. anthralin/tar/UVB in a day care treatment setting. Calcipotriol is synthetic vitamin D_3 analog indicated for the treatment of moderate plaque psoriasis. The 18 study patients had symmetric plaque-type psoriasis and had not been on systemic antipsoriatic agents for at least 3 months prior to enrollment. On one-half of the body, anthralin was applied with gradually increasing concentrations as tolerated. The other half-body received calcipotriol ointment twice daily. Both sides received UVB and additional coal tar distillate. Patients who were admitted to the day care program received UVB, anthralin, and calcipotriol on weekdays for two consecutive weeks. Clinical evaluations were completed at days 0 (baseline), 3, 7, 10, and 42[6]:

- The primary end-point was day 10.
- Anthralin and calcipotriol were found to be equally effective with approximately 50% clearing of lesions for each treatment at day 10. Therapy continued 4 weeks after day 10.
- Eleven patients presented for follow-up and no difference between treatment groups was detected.
- Fifteen patients completed the patient preference questionnaire. Patients rated calcipotriol as more effective ($p = 0.01$), anthralin as more irritating ($p = 0.001$) and 11 of the 15 patients preferred calcipotriol over anthralin ($p = 0.001$).

Swinkels et al found that the application of the high potency steroid, clobetasol 0.05% ointment, minimized irritation caused by anthralin.[7] Other approaches, such as short contact application of anthralin three times weekly versus five times weekly have been studied. McBride et al found that three times weekly application of anthralin was as effective as a five times weekly anthralin regimen when used in conjunction with UVB administered five times weekly. No difference in the frequency or severity of burning episodes was noted.[8]

The following table summarizes comparisons among topical corticosteroids, coal tar and anthralin.

Table 5. – Comparison of Topical and Intralesional Therapy with Steroids, Coal Tar and Anthralin [2]				
	Effectiveness	**Remission**	**Possible Side Effects**	**Comments**
Topical corticosteroids				
Mild potency	+	+	+AB	Ab
Mid potency	++	+/++	++AB	Abcd
Maximum potency	+++	++	+++AB	Abcdf
Intralesional steroids	+++	+++	++C	Bc
Coal Tar	**++**	**++**	**+ADE**	**Def**
Anthralin	**++**	**++**	**++ADE**	**Df**

Effectiveness: +, mild; ++, moderate; +++, high. Remission: +, <1 month; ++, 1-3 months; +++, >3 months. Possible side effects: +, mild; ++, moderate; +++, severe.

Possible Side Effects: A, Inconvenience; **B**, topical corticosteroid side effects may be local and/or systemic and may include burning, irritation, itching, stinging, erythema, folliculitis, skin atrophy, telangiectasia, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration, secondary infection, striae, miliaria, HPA axis suppression, hyperglycemia, hyperglycuria, and manifestations of Cushing's syndrome; side effects tend to increase with increased potency; **C**, pain, discomfort, atrophy, telangiectasia, and hypopigmentation; **D**, staining; **E**, irritation.

Comments: a, Tachyphylaxis; b, increased risk of steroid side effects with increased potency, duration of treatment, and total dosage; c, possibility of systemic absorption may limit use in children; d, avoid eye contact and intertriginous use in children; e, increased photosensitivity; f, avoid use in body folds.

Additional Evidence

Dose Simplification: Adherence to topical treatments is important in the treatment of psoriasis. Tars are reasonable treatments for most patients who have less than severe disease.[9] The modified tar or gels have much better patient acceptance and compliance because of decreased odor, staining, and messiness. Topically applied medications such as topical corticosteroids, salicylic acid, tar and dithranol preparations, as well as calcipotriol and tazarotene, are the favored first-line therapeutic options in the elderly.[10]

Stable Therapy: No peer reviewed studies were found in a literature search of Medline/Pubmed and Ovid on changing from coal tar or anthralin to other topical treatments for psoriasis.

Impact on Physician Visits: In a study to quantify resources used for the treatment of atopic dermatitis/eczema, member populations of private insurance were compared to those of a Medicaid population.[11] Medicaid patients used outpatient hospital visits and hospitalizations at a greater rate than did privately insured patients. A second study evaluated the utilization of medical services for psoriasis and found that visits to physicians in the United States made principally for psoriasis averaged 1.5 million per year.[12] Topical steroids were prescribed most often and systemic therapies at less than 10% of visits. The study found that the majority of patients make less than one visit per year to a physician for treatment.

A final study looked at the pattern of treatment of psoriasis and found that 80% or more of people with psoriasis do not see a physician for the disease in any given year.[13] Topical steroids were the only medication listed at 50% of psoriasis visits and were used in combination with another medication in an additional 26% of visits. Topical calcipotriene was the most commonly used noncorticosteroid treatment, and its use in combination with corticosteroids increased from 17% to 84% between 1994 and 1996.

IX. Conclusions

Head to head trials comparing the keratoplastics, coal tar and anthralin, were not identified. These two agents have comparable efficacy to topical steroids and calcipotriol in the treatment of psoriasis. These agents may be used in combination with one another or with other anti-psoriatics and photo-therapy. Both agents have staining properties and anthralin causes problematic skin irritation.

Therefore, all brand products within the keratoplastic class reviewed are comparable to each other and to the generics and OTC products in the class and offer no significant clinical advantage over other alternatives in general use.

X. Recommendations

No brand keratoplastic agent is recommended for preferred status.

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Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of the Topical Miscellaneous Skin and Mucous Membrane Agents
AHFS 843600
August 11, 2004

I. Overview

The topical miscellaneous skin and mucous membrane agents in AHFS class 843600 include products with a range of different indications. Table 1 includes agents included in this review and respective formulations and brand name examples. This review encompasses all dosage forms and strengths.

Table 1. Topical Miscellaneous Skin and Mucous Membrane Agents in this Review[1,2,3]

Generic Name	Formulation	Example Brand Name (s)
Alitretinoin	0.1% topical gel	Panretin
Acrylates/C10-30 alkyl acrylate crosspolymer, aloe vera extract, allantoin, cyclopentasiloxone, diazolidinyl urea, iodopropynyl butylcarbonate, dimethicone, disodium EDTA, glyceryl monosterate, isopropyl myristate, lipowax-D, mineral oil, myrito-312, propylene glycol, sodium hyaluronate, tocopherol, triethanolamine and water	170gm tube	RadiaPlexRX^
Aloe vera, flavor, fructose, maltodextrin, polyvinylpyrrolidone, potassium sorbate and sodium benzoate	Oral rinse powder	OramagicRX^
Balsam peru/castor oil/trypsin*	Trypsin, balsam peru and castor oil in varying strengths	Balsa-Derm, Granulderm, Granulex, TBC Xenaderm
Becaplermin	100UG/gm topical gel	Regranex
Bexarotene	1% topical gel	Targretin
Calcipotriene	0.005% topical cream, ointment and solution	Dovonex
Chloroxine	2% topical shampoo	Capitrol
Collagenase	250 units collagenase enzyme/gm topical ointment	Santyl
Diclofenac sodium	3% topical gel	Solaraze
Fibrinolysin w/desoxyribonuclease	10gm/gm, 666 units/gm, 1 unit/gm topical ointment	Elase
Fluorouracil*	0.5% topical cream	Carac
	5% topical cream and solution 2% topical solution	Efudex
	1% topical cream	Fluoroplex
Imiquimod	5% topical cream	Aldara
Polysorbate 20		Constant Clens
Pimecrolimus	1% topical cream	Elidel
Podofilox*	0.5% topical gel and solution	Condylox
Tacrolimus	0.03% and 0.1% topical ointment	Protopic
Tazarotene	0.5% an d0.1% topical cream and gel	Tazorac
Trichloroacetic acid	80% topical solution and bulk crystals	Tri-Chlor

*Generic Available. ^Classified by the FDA as a device.

II. Comparative Indications of the Topical Miscellaneous Skin and Mucous Membrane Agents

Table 2 includes each agent and their respective indication.

Table 2. FDA-Approved Indications for the Topical Miscellaneous Skin and Mucous Membrane Agents[1,2,3]

Generic Name	Example Brand Name (s)	Indication
Alitretinoin	Panretin	Kaposi's sarcoma cutaneous lesions
Refer to Table 1	RadiaPlexRX	Management of radiation dermatitis, partial and full thickness wound, first and second degree burns, cut and abrasions
Refer to Table 1	OramagicRX	Management of mucositis/stomatitis
Balsam peru/castor oil/trypsin	Balsa-Derm	Varicose ulcers, dehiscent wounds, decubital ulcers, sunburn and debridement of eschar Promote wound healing and for the treatment of decubitus ulcers, varicose ulcers and dehiscent wounds
	Granulderm	
	Granulex	
	TBC	
	Xenaderm	
Becaplermin	Regranex	Diabetic neuropathic ulcers
Bexarotene	Targretin	Cutaneous T-cell lymphoma
Calcipotriene	Dovonex	Psoriasis
Chloroxine	Capitrol	Treatment of dandruff and mild to moderately severe seborrheic dermatitis of the scalp
Collagenase	Santyl	Debriding chronic dermal ulcers and severely burned areas
Diclofenac sodium	Solaraze	Actinic keratoses
Fibrinolysin w/desoxyribonuclease	Elase	Debriding chronic dermal ulcers and severely burned areas
Fluorouracil	Carac	Multiple actinic or solar keratosis of face and anterior scalp areas
	Efudex	Multiple actinic or solar keratosis. The 5% strength is also indicated for superficial basal cell carcinomas when conventional methods are impractical
	Fluoroplex	Multiple actinic or solar keratosis
Imiquimod	Aldara	External genital and perianal warts, actinic keratosis, superficial basal cell carcinoma
Polysorbate 20	Constant Clens	Used to remove and soften necrotic tissue and debris
Pimecrolimus	Elidel	Mild to moderate atopic dermatitis
Podofilox	Condylox	Gel – anogenital warts (external genital and perianal warts Solution – external warts (*Condylomata acuminata*)
Tacrolimus	Protopic	Moderate to severe atopic dermatitis
Tazarotene	Tazorac	Psoriasis
Trichloroacetic acid	Tri-Chlor	Removal of verrucae; the CDC recommends therapy as an alternative regimen to cryotherapy for treatment of external genital/perianal warts and vaginal and anal warts

III. Pharmacokinetic Parameters

The available pharmacokinetic data for the miscellaneous skin and mucous membrane agents are included in Table 3. For the most part, minimal drug is absorbed from application of these agents.

Table 3. Pharmacokinetic Parameters of the Topical Miscellaneous Skin and Mucous Membrane Agents[1,2,3]

Agent	Bioavailability	Elimination	Protein Binding
Alitretinoin			
RadiaPlex RX			
OramagicRX			
Balsam peru/castor oil/trypsin			
Becaplermin	Variable[1]		
Bexarotene			
Calcipotriene	5-6%	Hepatically converted to inactive metabolite within 24 hours	
Chloroxine			
Collagenase			
Diclofenac sodium	≤ 10%	263ml/min $T_{1/2}$=1-2 hours	Tightly bound to albumin
Fibrinolysin w/desoxyribonuclease Elase			
Fluorouracil	< 5-10%		
Imiquimod	Minimal	< 0.9% of dose excreted in urine and feces	
Constant Clens			
Pimecrolimus	Limited absorption with no accumulation	< 1% of unchanged drug recovered in feces	74-87%
Podofilox	Dose-dependent[2]	$T_{½}$ = 1-4.5 hours	
Tacrolimus	Unknown		
Tazarotene	≤ 5%	$T_{½}$ = 18 hours	99%
Trichloroacetic acid			

[1] Ten patients with Stage III or IV lower-extremity diabetic ulcers received doses of 0.32 to 2.95mcg/kg once daily for 14 days. Six patients had undetectable absorption, two patients had PDGF levels at baseline but did not increase and two patients had PDGF levels increase sporadically from their baseline levels.

[2] Topical application of 0.05ml of 0.5% did not result in detectable serum levels while 0.1 to 1.5ml resulted in 1-17ng/ml 1-2 hours after application

IV. Drug Interactions of the Topical Miscellaneous Skin and Mucous Membrane Agents[1,2,3,4]

Agents within this class are minimally absorbed, therefore, there is little concern for drug interactions when these agents are used.

Bexarotene

No formal drug interaction studies have been conducted with bexarotene but oxidative metabolites appear to be formed by cytochrome P450 (CYP) 3A4. Drugs that induce (e.g., rifampin, phenytoin) or inhibit (e.g., erythromycin, fluconazole, calcium channel blockers) this enzyme may cause either a decrease or increase, respectively, in bexarotene concentrations.

Tacrolimus

No formal drug interaction studies have been conducted but it is recommended that concomitant administration of known CYP3A4 inhibitors (e.g., erythromycin, fluconazole, calcium channel blockers) with tacrolimus be done with caution. Based on minimal extent of absorption of topical tacrolimus, interactions with systemically administered drugs are unlikely to occur but cannot be ruled out.

Pimecrolimus

Drug-drug interaction studies with pimecrolimus have not been systematically evaluated but it is recommended that concomitant administration of known CYP3A4 inhibitors (e.g., erythromycin, fluconazole, calcium channel blockers) with pimecrolimus be done with caution. Again, due to very low blood levels in patients after pimecrolimus topical administration, systemic drug interactions are not expected, but cannot be ruled out.

V. Adverse Drug Events of the Topical Miscellaneous Skin and Mucous Membrane Agents

Tables 4 and 5 include reported adverse drug events for the respective miscellaneous skin and mucous membrane agents.

Table 4. Selected Topical Miscellaneous Skin and Mucous Membrane Agents Adverse Drug Events (%)

Adverse Drug Event	Agent								
	Alitretinoin	Becaplermin	Calcipotriene	Diclofenac	Fluorouracil	Imiquimod	Podofilox Sol	Podofilox Gel	Tacrolimus
Acne									0-7
Application site reaction				75-84	95				
Bleeding								1-19	
Burning, itching, skin irritation			10-15		75	9-26	64-78	12-37	26-58
Contact dermatitis				19-33					
Dryness				25-27	83				
Edema	6-8				35	12-17			
Erythema, dry skin, peeling, rash, dermatitis, worsening of psoriasis			1-10						
Exfoliative dermatitis	7-8			6-24					
Excoriation/tingling						18-25			
Erosion					44	29-30	67	9-27	
Erythema					93	54-61			9-28
Folliculitis									6-11
Fungal dermatitis									2-6
Fungal Infection						2-11			
Headache				0-7		4-5			5-20
Herpes simplex									0-12
Inflammation							63-71	9-32	
Irritation					1				
Influenza-like symptoms				1-10					22-35
Myalgia									
Pain	0-25			15-26	44	2-8	50-72	12-24	
Paresthesia	2-61			8-20					
Pruritis	8-22			31-52		22-32	50-65	8-32	25-46
Pustular rash									2-8
Rash	58-69	2		35-46					2-5
Scabbing						4-13			
Skin disorder	0-6								
Skin infection									5-12
Skin tingling									1-8
Urticaria									5-6

Table 5. Pimecrolimus Treatment Emergent Adverse Events (≥ 5%)

Adverse Drug Event	Study 1*		Study 2^	Study 3[&]		Study 4[#]
	Pimecrolimus	Vehicle	Pimecrolimus	Pimecrolimus	Vehicle	Pimecrolimus
> 1 ADE	68	71	72	85	75	78
Dermatological						
Skin Infection NOS	3	5	5	2	4	6
Impetigo	2	2	4	4	5	2
Folliculitis	1	1	1	2	4	6
GI						
Gastroenteritis NOS	0	2	1	7	3	2
Abdominal pain, upper	4	4	3	6	7	0
Sore throat	3	4	5	8	5	4
Vomiting	3	4	4	7	8	1
Diarrhea NOS	1	1	1	8	5	2
Nausea	0	2	1	4	7	2
Respiratory						
Upper respiratory tract infection NOS	14	13	19	5	8	4
Nasopharyngitis	10	7	20	27	21	8
Pharyngitis NOS	1	2	1	8	3	1
Bronchitis	0	2	1	11	8	2
Cough	12	8	9	16	11	2
Rhinitis	0	0	2	4	7	2
Special Senses						
Ear infection	2	2	6	3	1	1
Otitis media	2	1	3	3	5	1
Miscellaneous						
Influenza	3	1	7	13	4	10
Tonsillitis	0	0	1	6	0	1
Viral infection	1	1	0	7	0	0
Application site burning	10	13	2	9	7	26
Pyrexia	8	9	12	13	5	1
Application site reaction	3	5	2	3	3	15
Application site irritation	3	6	1	0	4	6
Hypersensitivity	4	4	5	5	1	3
Headache	14	9	11	25	16	7

*Study 1 was a 6-week vehicle-controlled trial comparing pimecrolimus (n=267) vs. vehicle (n=136) in pediatric patients
^Study 2 was a 20-week open-label trial (n=335) in pediatric patients
[&]Study 3 was a 1-year vehicle-controlled trial comparing pimecrolimus (n=272) vs. vehicle (n=75) in pediatric patients
[#]Study 4 was a 1-year comparator trial (n=328) in adult patients

Tazarotene Cream

10% to 23% - pruritus, erythema, burning

< 10% - irritation, desquamation, stinging, contact dermatitis, dermatitis, eczema, worsening of psoriasis, skin pain, rash, hypertriglyceridemia, dry skin, inflammation, peripheral edema

Tazarotene Gel

10% to 30% - pruritus, burning/stinging, erythema, worsening of psoriasis, irritation, skin pain

1%-10% - irritation, skin pain, fissuring, localized edema, skin discoloration

VI. Dosing and Administration of the Topical Miscellaneous Skin and Mucous Membrane Agents

Table 6 details the dosing and administration for each of the miscellaneous skin and mucous membrane agents.

Table 6. Dosing for the Topical Miscellaneous Skin and Mucous Membrane Agents[1,2,3]

Generic Name	Example Brand Name (s)	Dosing
Alitretinoin	Panretin	Initially apply twice daily and administration may be increased up to 3-4 times daily according to lesion tolerance. Continue therapy as long as benefit is derived.
Refer to Table 1	RadiaPlexRX	Apply to the radiation area four times daily.
Refer to Table 1	OramagicRX	Use as a rinse up to four times daily as needed.
Balsam peru/castor oil/trypsin	Balsa-Derm, Granulderm, Granulex, TBC Xenaderm	Apply once or twice daily. Before each application, the wound should be cleansed.
Becaplermin	Regranex	Apply one daily to ulcer. Amount of becaplermin is dependent upon ulcer size and becaplermin tube size. Each square inch of ulcer are requires about 2/3 inch length of gel squeezed from a 7.5 or 15 gm tube or about 1 1/3 inch length from a 2 gm tube. Each square centimeter ulcer surface requires approximately 0.25cm length of gel squeezed from a 7.5 or 15gm tube or 0.5cm from a 2 gm tube. Cover with a saline-moistened dressing for 12 hours after which time a second moist dressing should be applies. Continue treatment until complete ulcer healing.
Bexarotene	Targretin	Apply daily every other day for the first week. Increase the application frequency at weekly intervals to once daily, then twice daily, then three times daily, and finally 4 times daily according to individual lesion tolerance. A response is usually seen within 4 weeks and bexarotene has been used up to 172 weeks in clinical trials.
Calcipotriene	Dovonex	Apply a thin layer to affected skin twice daily; rub in gently and completely.
Chloroxine	Capitrol	Massage into wet scalp and allow lather to remain on scalp for 3 minutes then rinse; repeat application and rinse. Two applications per week are usually sufficient.
Collagenase	Santyl	Apply once daily directly to wound or to sterile gauze pad and apply pad to wound. Prior to each application, clean lesion of debris and digested material. If infection is present apply a topical antibiotic prior to collagenase. Cross-hatching may be necessary for the thick eschar, with a #10 blade.
Diclofenac sodium	Solaraze	Apply twice daily for 60 to 90 days.
Fibrinolysin w/desoxyribonuclease	Elase	Apply layer to affected area and cover with dressing three times daily.
Fluorouracil	Carac	Apply a thin film to affected area(s) once daily. Apply ten minutes after area is cleansed and dried. Continue treatment for 2-4 weeks.

	Efudex	Actinic or Solar Keratosis Apply twice daily in an amount sufficient to cover the lesion for 2-4 weeks. Superficial Basal Cell Carcinoma Apply twice daily in an amount sufficient to cover the lesion for 3-6 weeks.
	Fluoroplex	Apply twice daily in an amount sufficient to cover the entire face or affected areas for 2-6 weeks.
Imiquimod	Aldara	Apply 3 times weekly prior to normal sleeping hours and leave on the skin for 6-10 hours. Wash the treated area with mild soap and water after the treatment period. Therapy should be continued for a maximum of 16 weeks.
Polysorbate 20	Constant Clens	Use to cleanse the would once or twice daily.
Pimecrolimus	Elidel	Apply a thin layer twice daily and rub in gently and completely. Therapy may be continued as long as symptoms persist.
Podofilox	Condylox	Apply twice daily for 3 consecutive days, then discontinue for 4 days. The one week treatment cycle may be repeated until there is no visible wart tissue or for a maximum of 4 treatment cycles. Treatment should be limited to $\leq 10cm^2$ of wart tissue and to no more than 0.5GM's per day.
Tacrolimus	Protopic	Apply to affected area twice daily. Treatment should be continued for one week after atopic dermatitis is cleared.
Tazarotene	Tazorac	Apply a thin film to psoriatic lesions once daily in the evening.
Trichloroacetic acid	Tri-Chlor	Apply a small amount to the wart weekly.

Special Dosing Considerations

- Alitretinoin: No special population dosage recommendations are needed. This drug is a pregnancy category D, meaning teratogenecity and embryotoxicity has been demonstrated in animals receiving the oral drug. No actual reproduction studies have been done with the topical product. Safety and efficacy in children younger than 18 years of age have not been established.
- Becaplermin: Pregnancy category C. Safety and efficacy in children less than 16 years has not been established.
- Bexarotene: Pregnancy category X. Safety and efficacy in pediatric patients has not been established.
- Calcipotriene: Pregnancy category C. Safety and efficacy have not been established in children. Because of a higher ratio of skin surface area to body mass, children are at greater risk than adults of systemic adverse effects when they are treated with topical medication.
- Chloroxine: Pregnancy category C. Safety and efficacy for use in children has not been established.
- Collagenase: Safety and efficacy of collagenase in pediatric patients has not been established.
- Diclofenac: No special dosage recommendations are needed. Pregnancy category B. Use in the third trimester should be avoided because of possible premature closure of the ductus arteriosus. Use should also be avoided late in pregnancy because of possible delay in labor or parturition. Safety and efficacy has not been established in children; actinic keratoses generally are not seen in the pediatric population. Diclofenac sodium gel should not be used by children. The manufacturer also recommends caution in patients with severe renal and hepatic impairment
- Fluorouracil: Do not use Carac in patients with DPD enzyme deficiency. A large percentage of fluorouracil is catabolized by the enzyme DPD. DPD enzyme deficiency can result in shunting of fluorouracil to the anabolic pathway, leading to cytotoxic activity and potential toxicities. In vitro and in vivo studies of fluorouracil have shown positive effects for fertility impairment. Pregnancy category X.
- Imiquimod: For use in patients 12 years of age and older. Pregnancy category B.
- Pimecrolimus: Indicated for use in nonimmunocompromised patients ≥ 2 years of age in whom the use of alternative, conventional therapy is deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or intolerant of alternative, conventional therapies. Pregnancy category C.

- Podofilox: Pregnancy category C. Safety and efficacy in children has not been established.
- Tacrolimus: Pregnancy category C. Tacrolimus 0.03% ointment may be used in children ≥ 2 years of age. The drug is indicated for short-term and intermittent long-term therapy in the treatment of patients with moderate-to-severe atopic dermatitis in whom the use of alternative, conventional therapies are deemed inadvisable because of potential risks, or in the treatment of patients who are not adequately responsive to or are intolerant of alternative, conventional therapies.
- Tazarotene: Pregnancy category X. Safety and efficacy have not been established in patients under 18 years of age with psoriasis (cream), while safety and efficacy with the gel have not been established in patients less than 12 years of age.

VII. Comparative Effectiveness of the Topical Miscellaneous Skin and Mucous Membrane Agents

Table 7 describes recent comparative studies for selected drugs in this class.

Table 7. Outcomes Evidence for Selected Topical Miscellaneous Skin and Mucous Membrane Agents

Study	Sample	Duration	Results
Panretin Gel North America Study Group[5]	n=268	12 week, multicenter, randomized, double-blind, vehicle-controlled	In evaluating the efficacy of alitretinoin 0.1% (n=134) vs. vehicle gel (n=134) in the treatment of Kaposi's sarcoma (KS): • 35% vs. 18% response rate for alitretinoin vs. vehicle, respectively (p=0.002). • Time to first response shorter with alitretinoin (p=0.001) • Withdrawal rate of 31% and 25% for alitretinoin and vehicle groups, respectively (NS).
Efficacy and safety of becaplermin in patients with chronic neuropathic diabetic ulcers[6]	n=382	20 week, multicenter, double-blind, placebo-controlled phase II trial	Patients with Type I or II diabetes and chronic ulcers of at least 8 weeks' duration were randomized to becaplermin 30ug/g, 100ug/g or placebo: • Compared to placebo, becaplermin 100ug/g had a higher rate of complete healing (p=0.007) while 30ug/g did not. • Becaplermin 100ug/g also decreased the time to achieve complete healing vs. placebo (86 days vs. 127 days, respectively; p=0.013) • Similar discontinuation rates for all three groups
Diabetic ulcer study group[7]	n=118	20 week, multicenter, double-blind, placebo-controlled trial	Patients with chronic, full-thickness, lower extremity diabetic ulcers of at least 8 weeks' duration randomized to becaplermin or placebo: • 48% of becaplermin treated patients achieved completed wound healing vs. 25% in the placebo group (p=0.01) • No difference in the median reduction in wound area • No difference in ADE incidence
Phase 1 and 2 trial of bexarotene gel for skin-directed treatment of patients with cutaneous T-cell lymphoma[8]	n=67	20 week, open-label, dose-escalation clinical trial	Adults with early-stage (TNM stages 1A-IIA) CTCL were administered bexarotene gel 0.1%, 0.5% and 1.0% in incremental dosage adjustments from once to four times daily. • Adverse events were generally mild to moderate in severity and were confined to treatment sites. • Patients achieved an overall response rate of 63% and a clinical complete response rate of 21%. • Median projected time to onset of response was 20.1 weeks (range, 4.0-86.0 weeks), and the estimated median response duration from the start of therapy was 99 weeks. • Patients with no previous therapy for mycosis fungoides responded at a higher rate (75%) than those who previously underwent topical therapies (67%).
Calcipotriol vs coal tar in stable plaque psoriasis (SPP)[9]	n=36	12 week, prospective, right-left randomized, investigator-blinded study	Patients with bilateral SPP on limbs were instructed to apply a 5% coal tar ointment to one side and calcipotriol 0.005% to the other side: • Calcipotriol response rates at 4, 6, and 8 weeks significantly higher than for coal tar (p<0.01). • No difference in clinical response at 10 and 12 weeks or relapse rates.
Tazarotene Cream Clinical	n=1,303	Combined results of 2 multicenter, double-blind,	Patients were randomized to either tazarotene 0.05%, 0.1% or vehicle cream for 12 and 24 weeks:

Study Group[10]		randomized, vehicle-controlled studies	• Significantly higher success rates for tazarotene 0.1% at all evaluation periods compared to vehicle ($p \leq 0.034$). • Tazarotene 0.05% had higher success rates at 4-24 weeks in Study 1 and at 2-12 weeks in study 2 when compared to vehicle ($p \leq 0.038$). • Significantly greater reductions in plaque elevation, psoriatic lesion scaling, and global response for both strengths of tazarotene. • Significantly more treatment-related adverse events reports with tazarotene
Calcipotriol vs tazarotene with UVB in patients with severe psoriasis[11]	n=10	Comparative treatment study	Patients were instructed to apply calcipotriol ointment and tazarotene 0.05% gel to each side of their body. Patients also received UVB (311nm) once daily, four times a week. After a median 19 UVB treatment sessions results were: • Similar decreases in Psoriasis Area and Severity Index score at 4 weeks.
Topical treatment of actinic keratoses with 3% diclofenac in 2.5% hyaluronan.[12]	n=195	12 week, multicenter, double-blind, placebo-controlled study	Patients were randomized to one of four treatment groups (i.e., 30 or 60 days of active treatment administered twice daily or 30 or 60 days of placebo): • Significantly more patients give active treatment for 60 days had target and cumulative lesion number scores and total thickness scores of zero vs. placebo. • The patient global improvement indices were also significantly better in the active treatment groups. • Therapy was well tolerated and incidence of ADE's was similar between active treatment and placebo groups.
Photodynamic therapy and topical 5-FU for actinic keratoses[13]	n=17	24 week, randomized, paired-comparison trial	Each patient's right and left hands were randomized to receive either a 3-week course of topical 5-FU applied BID or photodynamic using 5-aminolevulenic acid and then, after 4 hours, irradiation: • No statistical difference in mean reduction of lesion area and overall symptom scores for pain and redness
Imiquimod for external genital and perianal warts[14]	n=209	16 week, randomized, double-blind, vehicle-controlled	Patients were instructed to apply either active treatment or the vehicle cream 3 times weekly for 8 hours during normal sleeping hours: • 50% of patients treated with imiquimod experienced complete clearance while only 11% in the vehicle group did. • When examined by gender, complete clearance rates were significantly higher in the active treatment group. • Clearance was independent of wart size. • Efficacy in patients who had undergone previous wart treatment (e.g., podophyllin or cryotherapy) was statistically more effective in the active treatment group.
Long-term management of atopic dermatitis in infants with topical pimecrolimus[15]	n=251	1 year, double-blind, controlled study	Infants aged 3-23 months received either pimecrolimus or conventional therapy (emollients and short-term treatment of flares with moderately potent topical corticosteroids): • Pimecrolimus associated with a significantly lower incidence of flares. • 57% of pimecrolimus-treatment patients without a flare at 12 months compared to 28% in the conventional therapy group ($p<0.001$). • Pimecrolimus associated with a longer flare-free period ($p<0.001$) • Mean number of flares lower in pimecrolimus group ($p<0.001$) • At month 6, a significantly higher of pimecrolimus-treated group had clear or nearly clear skin compared to conventional therapy. • Both treatments were well tolerated.
Tacrolimus vs. hydrocortisone in children with atopic dermatitis[16]	n=560	5 week, phase III, comparative, multicenter, randomized, double-blind, parallel group study	Patients 2-15 years of age received either tacrolimus 0.03% or 0.1% or hydrocortisone 1% applied twice daily: • Tacrolimus 0.0.3% and 0.1% significantly more effective than hydrocortisone with regards to the modified eczema area and severity index median as a percent of baseline. • Physician's global evaluation was also statistically higher for tacrolimus. • Transient skin burning higher in tacrolimus group. • No treatment differences in lab parameters.
Tacrolimus vs. hydrocortisone butyrate 0.1% in adult patients[17]	n=570	3-week, phase III, comparative, multicenter, randomized, double-blind, parallel-group	Patients with moderate to severe atopic dermatitis over $\geq$ 5% of total body surface area were randomized to receive either tacrolimus 0.03%, tacrolimus 0.1% or hydrocortisone butyrate 0.1% applied twice daily to affected areas: • No difference in modified eczema area and severity index (mEASI) or in the physician's global evaluation clinical response between tacrolimus 0.1% and hydrocortisone. Both hydrocortisone and tacrolimus 0.1% had improved outcomes over 0.03%.

			• Application site skin burning and pruritis higher in tacrolimus group ($p<0.05$). • No difference in laboratory parameters (hematology and clinical chemistry)
Xenaderm ointment vs. Granulex spray vs. saline for wound treatment[18]	n=30	10 day randomized controlled study of experimentally induced skin wounds	A YAG laser was used to create partial-thickness wounds on the right and left thigh approximately 6 mm in diameter. Each participant served as his/her own control. • At day 3, erythema was significantly lower in the ointment treated wounds and continued to be significantly lower throughout the course of the study ($P<0.05$). • Edema was significantly lower ($P<0.05$) at wound sites treated with the ointment than wounds treated with the spray at day 1 and continued to be lower through day 7. • Scabbing was significantly reduced ($P<0.05$) at day 1 in wounds treated with the ointment and continued to be so throughout the course of the study. • Re-epithelialization of the wound was greater in wounds treated with the ointment. By day 3, the difference in favor of the ointment was significant ($P<0.05$), and at successive observation days, the differences continued to favor the ointment by a widening margin ($P<0.05$).

Pressure Ulcer Prevention and Treatment Clinical Guidelines[19]
Although the trypsin/balsum peru/castor oil preparations are indicated for the debridement of different ulcers, these guidelines do not discuss these preparations in debridement of pressure ulcers and recommends they not be used for wound cleansing because they may be toxic to human fibroblasts. These guidelines do discuss the use of enzymatic debridement with collagenase and recommends this therapy be considered when patients are unable to tolerate surgery or are in long-term care facilities or receiving care at home. This therapy should only be used if the ulcer is not infected.

Seborrheic dermatitis[20]
Treatment modalities for seborrheic dermatitis include keratolytics, corticosteroids and antifungals. At the time of this review, no placebo-controlled or comparative clinical trials using cloroxine could be found.

Sexually Transmitted Disease Treatment Guidelines 2002[21]
The primary goal of treating external genital warts caused by *Human papillomavirus*, is the removal of symptomatic warts. While present therapies reduce infectivity, they probably do not eradicate the virus. There is no definitive evidence that one therapy is superior to others or that a single treatment is suitable for all patients. Recommended patient-applied regimens include either podofilox 0.5% solution or gel or imiquimod 5% cream. Alternative provider-administered therapies include cryotherapy, podophyllin resin or trichloroacetic acid.

Additional Evidence

Dose Simplification: Some treatments in this class are the only topical treatments for their respective indications (Panretin, Regranex, Targretin, Santyl). Therefore, there is limited opportunity for dose simplification for many of these agents. The treatments for psoriasis and atopic dermatitis are administered once or twice daily, while the therapies for genital warts are administered similarly (three times weekly). A study evaluated patient compliance with psoriasis treatment.[25] The overall mean +/- SD medication adherence was 60.6% +/- 33.0%. Being female, married, employed, and not paying for prescriptions were characteristics associated with increased medication adherence. Medication adherence was greater for topical or combined therapy, for once-daily treatment, and for first-time use of treatment. Adverse events reduced compliance. Patients with facial disease and with more extensive disease had lower medication adherence. No peer reviewed studies were found in a literature search of Medline/Pubmed and Ovid evaluating patient adherence with therapies for genital warts.

Stable Therapy: No studies were found in a literature search of Medline/Pubmed and Ovid that evaluated switching from either pimecrolimus or tacrolimus. One study has looked at the clinical benefit of switching patients with plaque psoriasis from calcipotriene to tazarotene.[26] In a group of 166 patients switched from calcipotriene with or without a topical corticosteroid, to tazarotene, the group experienced substantial additional improvements in efficacy and patient satisfaction

over and above those already achieved with calcipotriene +/- corticosteroid treatment. The mean scores for overall severity of plaque psoriasis, plaque elevation, scaling, pruritus, and overall discomfort were reduced by 35%, 41%, 44%, 45%, and 40%, respectively, compared with baseline levels at the time of switching therapy. The severity of each of these parameters was reduced from mild-to-moderate at baseline to trace-to-mild after a mean of 10 weeks treatment with tazarotene plus a corticosteroid.

Impact on Physician Visits: See the Impact on Physician Visits section of the Keratoplastics review for a discussion of the treatment of psoriasis and physician visits. See also the Impact on Physician Visits section of the Keratolytics review for a discussion of the treatment of genital warts and physician visits. A literature search of the Medline/Pubmed and Ovid database did not reveal data on the impact of tacrolimus or pimecrolimus on physician visits and/or medical resource utilization.

VIII. Conclusions

The topical miscellaneous skin and mucous membrane agents have a wide range of indications with seven agents having comparable indications. While no studies were available for some of the agents (e.g., OramagicRX, Constant Clens and RadiaPlexRX), others had a small sample size or were placebo-controlled trials. Nevertheless, some clinical guidelines make specific recommendations pertaining to these respective agents' place in treatment. Additionally, some agents have generic formulations (e.g., fluorouracil, balsam peru/trypsin/castor oil topicals and podofilox).

Calcipotriene and tazarotene are both indicated in the treatment of psoriasis. In the comparative studies included in Table 7, calcipotriene did better than coal tar in short-term outcomes but no difference was seen in either clinical response at 10 and 12 weeks or relapse rate. In another study, tazarotene had better outcomes than a vehicle comparator. There was only one small study (n=10) that compared calcipotriene and tazarotene. This study reported no difference in outcomes between the agents. Additionally, other studies have not shown a clear clinical advantage for either calcipotriene or tazarotene over topical corticosteroids.[21-24]

Imiquimod, podofilox and trichloroacetic acid are indicated for the treatment of genital warts. While no head-to-head trials could be found, the STD treatment guidelines recommend patient-applied podofilox or imiquimod as first-line therapy for the treatment of genital warts and trichloroacetic acid be reserved as an alternative.

Pimecrolimus and tacrolimus are both indicated in the treatment of atopic dermatitis. Although topical corticosteroids have been a mainstay for anti-inflammatory treatment, there is concern, due to potential side effects, with their chronic use. While both pimecrolimus and tacrolimus have been shown to be more efficacious than other therapies in children, one study reported improved outcomes for hydrocortisone 0.1% vs. tacrolimus 0.03% and no difference between hydrocortisone 0.1% and tacrolimus 0.1% ointment in adults. Furthermore, no head-to-head trials comparing these agents could be found at the time of this review.

When comparing agents within the topical miscellaneous skin and mucous membrane agent class, alitretinoin, becaplermin, bexarotene, collagenase, diclofenac sodium, and fibrinolysin w/desoxyribonuclease offer significant clinical advantage when used for their respective treatment indications. At this time, there is not a role for these agents in general use. Because these six medications have narrow indications with limited usage, they should be available for special needs/circumstances that require medical justification through the prior authorization process. After clinical circumstances are explored, proper medical justification will provide patient access to these agents.

However, the remaining agents in this class are comparable to each other and to the generics and OTC products in this class and offer no significant clinical advantage over other alternative in general use.

IX. Recommendations

No brand miscellaneous skin and mucous membrane agent is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Pharmacotherapy Review
Inspra (Eplerenone) – Mineralocorticoid (Aldosterone) Receptor Antagonist
AHFS Class 243220 (A subset review of diuretics 402800)
August 11, 2004

I. Overview

Activation of the renin-angiotensin-aldosterone system (RAAS) is responsible for adverse outcomes in patients with hypertension and heart failure.[1] One component of the RAAS, aldosterone, produces a number of deleterious effects on the cardiovascular system, including myocardial necrosis and fibrosis, vascular stiffening and injury, reduced fibrinolysis, endothelial dysfunction, catecholamine release, and production of cardiac arrhythmias.[2] Aldosterone synthesis occurs primarily in the adrenal gland and is modulated by multiple factors, including angiotensin II and non-RAAS mediators such as adrenocorticotropic hormone (ACTH) and potassium. Aldosterone binds to mineralocorticoid receptors in both epithelial (e.g., kidney) and nonepithelial (e.g., heart, blood vessels, and brain) tissues and increases blood pressure through induction of sodium reabsorption and possibly other mechanisms.[3]

Blockade of aldosterone receptors decreases blood pressure and produces cardioprotective effects.[4-12] The clinical importance of spironolactone, an aldosterone receptor blocker, has been demonstrated in the treatment of hypertension and heart failure. The Randomized Aldactone Evaluation Study (RALES) proved that antagonism of aldosterone had an important role in the management of heart failure, including patients taking angiotensin-converting enzyme (ACE) inhibitors. In addition to reducing mortality by 30 percent, small doses of spironolactone resulted in an improvement in ventricular function and enhanced exercise tolerance.[4]

Eplerenone is the first selective aldosterone inhibitor and selectively binds to recombinant human mineralocorticoid receptors relative to its binding to recombinant human glucocorticoid, progesterone and androgen receptors.[3] Clinical studies have demonstrated its efficacy in the treatment of hypertension either as monotherapy or add on therapy.[5-11] The results of EPHESUS (Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) demonstrated a benefit with the addition of an aldosterone-receptor antagonist to the drug regimen of patients with LV dysfunction who were already receiving optimal medical therapy. Statistically significant reductions in hospitalizations and mortality were reported.[12] Because of its selective binding, eplerenone may be associated with fewer progestogenic and antiandrogenic adverse effects than spironolactone including gynecomastia, impotence, and menstrual irregularities.[5-12]

Eplerenone is currently available as the brand name product Inspra®. It is available in 25mg and 50 mg tablets and is not available as a generic. This review encompasses all dosage forms and strengths of the new drug. Eplerenone is being reviewed as a new product and a subset to the diuretics therapy class (AHFS 402800). The mineralocorticoid agents were newly classified into AHFS class 243220 in 2004. The diuretics therapy class was originally reviewed in December 2003; the previous diuretics pharmacotherapy review in full is available for reference in Appendix 1.

II. Current Treatment Guidelines

JNC VII recommends the use of aldosterone antagonists as add on therapy for hypertensive patients with specific comorbidities (e.g. post-MI or symptomatic ventricular dysfunction or end stage heart disease).[13] The American College of Cardiology/American Heart Association heart failure guidelines recommend consideration of the aldosterone antagonist, spironolactone (eplerenone was not available at the time of publication), in low doses in patients with class IV symptoms despite use of other agents (e.g., digoxin, diuretics, an ACE inhibitor, and a beta-blocker).[14]

III. Indications

a. **Congestive Heart Failure Post-Myocardial Infarction -** to improve survival of stable patients with left ventricular systolic dysfunction (ejection fraction $\leq$ 40%) and clinical evidence of congestive heart failure after an acute myocardial infarction.[3]
b. **Hypertension** – alone or in combination with other antihypertensive agents.[3]

IV. Pharmacokinetics

Absorption[3]:

- Mean peak plasma concentrations are reached approximately 1.5 hours following oral administration. The absolute bioavailability of eplerenone is unknown.
- Both peak plasma levels (Cmax) and area under the curve (AUC) are dose proportional for doses of 25 to 100mg and less than proportional at doses above 100mg.
- Food does not affect absorption.

Volume of Distribution and Protein Binding[3]:

- The plasma protein binding of eplerenone is about 50% and it is primarily bound to alpha 1-acid glycoproteins.
- The apparent volume of distribution at steady state ranged from 43 to 90L.

Metabolism and Elimination[3]:

- Eplerenone is cleared predominantly by cytochrome P450 (CYP) 3A4 metabolism.
- Elimination half- life: 4 to 6 hours.
- Steady state is reached within 2 days.
- Inhibitors of CYP3A4 (e.g., ketoconazole, saquinavir) increase blood levels of eplerenone.

Special Populations[3]:

The pharmacokinetics of eplerenone at a dose of 100mg once daily have been investigated in the elderly (≥65 years), in males and females, and in blacks:

- The pharmacokinetics of eplerenone did not differ significantly between males and females.
- At steady state, elderly subjects had increases in Cmax (22%) and AUC (45%) compared with younger subjects (18 to 45 years).
- At steady state, Cmax was 19% lower and AUC was 26% lower in blacks.

Renal insufficiency and in patients undergoing hemodialysis:

- Compared with control subjects, steady-state AUC and Cmax were increased by 38% and 24%, respectively, in patients with severe renal impairment and were decreased by 26% and 3%, respectively, in patients undergoing hemodialysis.
- No correlation was observed between plasma clearance of eplerenone and creatinine clearance.
- Eplerenone is not removed by hemodialysis.

Eplerenone 400mg was evaluated in patients with moderate (Child-Pugh Class B) hepatic impairment and compared with normal subjects:

- Steady-state Cmax and AUC of eplerenone were increased by 3.6% and 42%, respectively.

Eplerenone 50mg was evaluated in 8 patients with heart failure (NYHA classification II-IV) and 8 matched (gender, age, weight) healthy controls:

- Compared with the controls, steady state AUC and Cmax in patients with stable heart failure were 38% and 30% higher, respectively

V. Drug Interactions

Drug-drug interaction studies were conducted with a 100mg dose of eplerenone:
Eplerenone is metabolized primarily by CYP3A4. A potent inhibitor of CYP3A4 (ketoconazole) caused increased exposure of about 5-fold while less potent CYP3A4 inhibitors (erythromycin, saquinavir, verapamil, and fluconazole) gave approximately 2- fold increases.[3]

Concomitant use of potassium supplements or potassium- sparing diuretics (amiloride, spironolactone, or triamterene) with eplerenone is contraindicated.[3]

VI. Adverse Drug Events

With the exception of hyperkalemia, the adverse effect profile of eplerenone in clinical studies given alone or in combination with other antihypertensive medications was not significantly different from that of placebo.[5-12] The main risk of eplerenone is hyperkalemia. Hyperkalemia can cause serious, sometimes fatal, arrhythmias.[3] The increased incidence of hyperkalemia with eplerenone is similar to that seen during aldosterone-receptor antagonism with spironolactone therapy.[4,5] In clinical studies, rates of hyperkalemia with eplerenone increased with decreasing renal function. In all studies serum potassium elevations >5.5mEq/L were observed in 10.4% of patients treated with eplerenone with baseline calculated creatinine clearance <70mL/min, 5.6% of patients with baseline creatinine clearance of 70 to 100mL/min, and 2.6% of patients with baseline creatinine clearance of >100mL/min. Periodic monitoring is recommended in patients at risk for the development of hyperkalemia (including patients receiving concomitant ACE inhibitors or angiotensin II receptor antagonists).[3] Dose reduction has been shown to decrease potassium levels.

Patients with CHF post-myocardial infarction with serum creatinine levels >2mg/dL (males) or >1.8mg/dL (females) or creatinine clearance $\leq$50mL/min should be treated with caution.[3]

Diabetic patients with CHF post-myocardial infarction, including those with proteinuria, should also be treated with caution. Patients with both diabetes and proteinuria have been shown to have increased rates of hyperkalemia.[3]

Table 1[3]. Adverse Events Rates (%)*

	Eplerenone (Inspra) (n=945)	Placebo (n=372)
Body as a Whole		
Fatigue	2	1
Influenza-like symptoms	2	1
Metabolic		
Hypercholesterolemia	1	0
Hypertriglyceridemia	1	0
VII. Digestive		
VIII. Diarrhea	2	1
Abdominal pain	1	0
Urinary		
Albuminuria	1	0
Respiratory		
Coughing	2	1
Central/Peripheral Nervous System		
Dizziness	3	2

*Occurring in placebo–controlled hypertension studies in patients treated with eplerenone (25 to 400mg) and at a more frequent rate than in placebo-treated patients.

To date, the rate of sex hormone–related adverse events has been lower with eplerenone than with spironolactone.[4-12] Studies in hypertension and RALES found a dose-dependent incidence of gynecomastia or breast pain (up to 52%) in men receiving dosages of spironolactone up to 150mg/d.[1,4] The incidence of these effects was significantly greater in patients receiving spironolactone compared with those receiving placebo (10% vs 1%, respectively; $P < 0.001$). On the other hand, sex hormone–related events with eplerenone have been reported in up to 2.5% of patients,[1,6-7,10-12] although some studies reported no gynecomastia, breast pain, or menstrual abnormalities.[5,8-9] Head-to-head studies with eplerenone and spironolactone are needed to fully evaluate these differences in adverse events.

The product information states that eplerenone treatment may be associated with mild increases in cholesterol (mean change, –0.4 to 11.6mg/dL), triglycerides (mean change, 7.1 to 26.6mg/dL), uric acid (0.3% incidence of uric acid concentrations >9mg/dL), alanine aminotransferase (mean change, 0.8 to 4.8U/L), gamma-glutamyltransferase (mean change, 3.1 to 11.3U/L), and serum creatinine (mean change, 0.01 to 0.03mg/dL).[3] None of the published trials evaluating the safety and efficacy of eplerenone reported a statistical analysis of these changes or addressed their clinical significance.[1]

Table 2. Rates of Sex Hormone Related Adverse Events with Eplerenone in Hypertension Clinical Studies[1]

	Rates in Males		Rates in Females
	Gynecomastia	Mastodynia	Abnormal Vaginal Bleeding
Inspra	0.4%	0.1%	0.4%
Placebo	0.5%	0.1%	0.4%

VII. Dosing and Administration

Congestive Heart Failure Post-Myocardial Infarction
The recommended dose is 50mg once daily. Treatment should be initiated at 25mg once daily and titrated to the target dose of 50mg once daily preferably within 4 weeks as tolerated by the patient. Eplerenone may be administered with or without food.[3]

Hypertension
The recommended starting dose is 50mg administered once daily. The full therapeutic effect is apparent within 4 weeks. For patients with an inadequate blood pressure response to 50mg once daily, the dosage of should be increased to 50mg twice daily. Higher dosages are not recommended either because they have no greater effect on blood pressure than 100mg or because they are associated with an increased risk of hyperkalemia.[3]

Table 3. Indications and Recommended Dosing for Eplerenone[3]

Indication	Initial Dose	Maximum Dose
Congestive Heart Failure	25mg QD	50mg QD
Hypertension	50mg QD	50mg BID

No adjustment of the starting dose is recommended for the elderly or for patients with mild-to-moderate hepatic impairment. For patients receiving weak CYP3A4 inhibitors, such as erythromycin, saquinavir, verapamil, and fluconazole the starting dose should be reduced to 25mg once daily.[3]

Table 4. Dose Adjustment in Congestive Heart Failure[3]

Serum Potassium (mEq/L)	Action	Dosage Adjustment
< 5.0	Increase	25mg QOD → 25mg QD 25mg QD → 50mg QD
5.0-5.4	Maintain	No Adjustment
5.5-5.9	Decrease	50mg QD → 25mg QD 25mg QD → 25mg QOD 25mg QOD → withhold
≥ 6.0	Withhold	

Following withholding eplerenone due to serum potassium ≥ 6.0mEq/L, eplerenone can be restarted at a dose of 25mg QOD when serum potassium levels have fallen below 5.5mEq/L.[3]

Special Dosing Considerations

- The use of eplerenone in patients with severe hepatic impairment has not been evaluated. No dosage adjustment is needed for the elderly in those with mild-moderate hepatic impairment. The drug is considered pregnancy category B. The safety and efficacy of eplerenone have not been established in pediatric patients. Eplerenone is contraindicated in patients with a serum creatinine > 2mg/dL in males or 1.8mg/dL in females, or with a creatinine clearance less than 50ml/min. Data is not available pertaining to bioequivalence of the crushed tablets.
- In contrast, spironolactone is indicated in children and has been studied in this population. The tablets can be crushed and administered as an oral suspension in cherry syrup.

VIII. Effectiveness

Hypertension

The antihypertensive effects of eplerenone have been studied in a variety of patients including women, older patients (≥ 50 years) and black patients. Eplerenone decreases both systolic blood pressure (SBP) and diastolic blood pressure (DBP) to a greater extent than placebo.[5,6,8,9]

Weinberger et al[5] assessed the efficacy and safety profile of eplerenone in 409 patients with hypertension. Spironolactone was included as an active aldosterone-receptor antagonist control. Seated blood pressure was significantly reduced from baseline in the eplerenone once- and twice-daily groups compared with placebo. Changes in systolic blood pressure (SBP) and diastolic blood pressure (DBP) in the eplerenone groups ranged from –4.4 to –15.0mm Hg and –4.4 to –8.9mm Hg, respectively, compared with +1.6 and –1.1mm Hg in the placebo group. Seated blood pressure was also significantly reduced with spironolactone (SBP, –16.7mm Hg; DBP, –9.5mm Hg) compared with placebo ($P < 0.05$). While no statistical comparison was provided, blood pressure reductions were similar with eplerenone and spironolactone. The incidence of adverse effects with eplerenone appeared to be similar to that with placebo. Serum potassium concentrations were significantly increased from baseline in 4 of the 6 eplerenone groups and the spironolactone group compared with placebo ($P < 0.05$). Four percent of patients (17/409) had a serum potassium concentration >5.5mEq/L. Sex hormone–related adverse effects (e.g., gynecomastia, breast pain, impotence, menstrual abnormalities) were not reported in the eplerenone groups.[5]

In a 12 week study by White et al[6], the efficacy and tolerability of eplerenone 25, 50, 100, and 200mg once daily was evaluated in 400 patients with untreated hypertension. The adjusted mean changes in SBP and DBP were significant in the eplerenone groups compared with the placebo group ($P \leq 0.01$). In the group that received eplerenone 25mg, the reduction in DPB was not significant compared with placebo. Mean changes in SBP and DBP in the eplerenone groups ranged from –5.7 to –10.4mm Hg and –3.7 to –6.3mm Hg, respectively. Significant reductions also occurred in 24-hour ambulatory SBP and DBP in all eplerenone groups compared with placebo (SBP: $P \leq 0.006$; DBP: $P \leq 0.005$). Adverse effects were reported in 48% of eplerenone recipients and 49% of placebo recipients. One eplerenone recipient had a serum potassium concentration >5.5mEq/L, and 1 reported impotence.[6]

In a 24 week study by White, et al[7], eplerenone 50-200mg/day was compared to amlodipine 2.5-10mg/day in 269 patients ≥ 50 years of age with hypertension. After 24 weeks of therapy, similar reductions in SBP occurred for both treatments (eplerenone, -20.5 ±1.1mm Hg; amlodipine, -20.1 ±1.1mm Hg). Amlodipine produced significantly greater reductions in DBP (-6.9 ±0.7mm Hg) compared with eplerenone (-4.5 ±0.7mm Hg) (P=0.014).[7]

Flack et al[8] compared blood pressure reductions with eplerenone, losartan, and placebo in 551 white and black patients with hypertension. Compared with losartan and placebo, eplerenone was associated with significant reductions in SBP and DBP in all patients combined ($P < 0.001$) and in black patients ($P \leq 0.001$). In white patients, the mean changes in DBP and SBP were significant for eplerenone compared with placebo ($P = 0.001$) but not compared with losartan. SBP reductions in eplerenone recipients ranged from 10.5 to 14.9mm Hg, whereas the corresponding reductions in the losartan and placebo groups ranged from 3.9 to 10.3mm Hg and 2.4 to 5.2mm Hg. DBP reductions in eplerenone recipients

ranged from 9.3 to 12.2mm Hg, compared with corresponding reductions of 5.1 to 9.4mm Hg and 3.8 to 7.4mm Hg in the losartan and placebo groups. The incidence of adverse effects was not significantly different between eplerenone and losartan or placebo. There were no reports of impotence, gynecomastia, or breast tenderness in the eplerenone group; however, 2 patients reported menstrual irregularities, and 2 reported decreased libido.[8]

Concomitant use of eplerenone with an ACE inhibitor or an ARB provides added benefits. ACE inhibitors and ARBs target the renin-angiotensin-aldosterone system by either reducing the production of angiotensin II or by directly blocking its effects at the receptor site. While the activity of angiotensin II is significantly reduced, there is still production of aldosterone ("aldosterone escape"). Even the combination of ACE inhibitor and ARB does not completely eliminate aldosterone production.[1] Eplerenone, used as add-on therapy with ACE inhibitors or ARBs, has been shown to provide significant lowering of SBP in both groups and of DBP in ARB patients.[8,9] In an 8 week study, Krum et al[9] evaluated the efficacy and safety profile of eplerenone added to current ACE-inhibitor or ARB therapy in 341 patients with hypertension. Patients had mild to moderate hypertension unresponsive to current ACE-inhibitor or ARB therapy. By study end, mean seated DBP was significantly reduced from baseline among patients receiving eplerenone/ARB (-12.7±0.81mm Hg) compared with those receiving placebo/ARB (-9.3±0.83mm Hg). The change in mean seated DBP was -9.9±0.88mm Hg in eplerenone/ACE inhibitor patients and -8.0±0.86mm Hg in placebo/ACE inhibitor patients (*P*=NS). SBP levels were also significantly lower at week 8 for eplerenone/ACE inhibitor (-13.4 ±1.35mm Hg) and eplerenone/ARB (-16.0 ±1.37mm Hg) patients, respectively, compared with placebo/ACE inhibitor (-7.5 ±1.31mm Hg) and placebo/ARB patients (-9.2 ±1.41mm Hg). Adverse events were generally nonsevere and not significantly different between eplerenone and placebo. One patient in the eplerenone/ACE-inhibitor group had a serum potassium concentration >5mEq/L. No sex hormone–related adverse effects were reported in the eplerenone groups. This study demonstrated that in patients whose BP was not controlled with an ACE inhibitor or ARB, the addition of eplerenone over an 8-week period significantly lowered SBP in both groups and DBP in ARB patients.[9]

Data on the efficacy of eplerenone in hypertension are summarized in Table 5.

Table 5. Efficacy of Eplerenone in Hypertension: Clinical Study Results

Reference	Patient Characteristics	Study Design	Mean change in SBP/DPB, mm Hg
Weinberger et al[5]	n = 409; age 21–80 years; mild to moderate HTN (clinic DBP ≥95mm Hg and <114mm Hg, ambulatory DBP ≥85mm Hg)	R, DB,AC (SPL), PG; fixed doses of EPL 50, 100, or 400mg QD, EPL 25, 50, or 200mg BID, SPL 50mg BID, or placebo; primary efficacy variable was adjusted mean change in clinic DBP vs placebo	EPL 50mg: –4.4/–4.5* EPL 100mg: –7.9/–4.4* EPL 400mg: –15/–8.7* EPL 25mg BID: –8.1/–4.4*† EPL 50mg BID: –11.7/–7.8*† EPL 200mg BID: –14.8/–8.9*† SPL 50mg BID: –16.7/–9.5* Placebo: +1.6/–1.1
White et al[6]	n = 400; untreated HTN (SBP <180mm Hg, DBP 95–110mm Hg)	R, DB, PC, PG; EPL 25, 50, 100, or 200mg QD; primary efficacy variable was mean change in DBP at 12 wk	EPL 25mg: –5.7**/–3.7 EPL 50mg: –6.7**/–4.6** EPL 100mg: –10.4**/–6.3** EPL 200mg: –8.8**/–5.4** Placebo: 0/–1.7
White et al[7]	n = 269; mean age, 67.7 years; systolic HTN and/or widened PP (SBP ≥150mm Hg and <165mm Hg and PP ≥70mm Hg, or SBP ≥165mm Hg and <200mm Hg and DBP <95mm Hg)	R, DB; therapy initiated at EPL 50mg or AML 2.5mg QD; 2-step titration to EPL 100 and 200mg QD and AML 5 and 10mg QD to reduce SBP to ≤140mm Hg	Mean change in SBP, mm Hg EPL: –20.5 AML: –20.1 Mean change in PP, mm Hg EPL: –15.9 AML: –13.4
Flack et al[8]	n = 535; black and white; mild to moderate HTN (SBP <180mm Hg, DBP 95–109mm Hg)	R, DB, PC and AC (LOS), PG; primary efficacy variable was mean change in DBP at final visit (wk 16); titration to effect (EPL 50–200mg QD, LOS 50–100mg QD) based on DBP and SBP	All patients EPL: –12.8§‖/–10.3§‖ LOS: –6.3/–6.9 Placebo: –3.4/–5.3 Black patients EPL: –13.5§‖/–10.2§¶ LOS: –5.3/–6.0 Placebo: –3.7/–4.8 White patients EPL: –12.3#/–11.1# LOS: –8.5/–8.4 Placebo: –3.2/–6.4
Krum, et al[9]	n = 341; age 18-85 years; mild to moderate uncontrolled HTN at fixed dose of ACE inhibitor or ARB	R, DB, PC, PG; titration to effect (EPL 50-100mg QD), primary efficacy variable was mean change in DBP and SBP at 8 week	ACE-inhibitor group EPL: –13.4‡/–9.9 Placebo: –7.5/–8.0 ARB group EPL: –16‡/–12.7‡ Placebo: –9.2/–9.3

SBP = systolic blood pressure; DBP = diastolic blood pressure; HTN = hypertension; R = randomized; DB = double-blind; AC = active-controlled; SPL = spironolactone; PG = parallel-group; ACE = angiotensin-converting enzyme; ARB = angiotensin-receptor blocker; PC = placebo-controlled; LOS = losartan; ENAL = enalapril; BP = blood pressure; HCTZ = hydrochlorothiazide; PP = pulse pressure; AML = amlodipine.
*$P < 0.05$ versus placebo.
†$P < 0.05$ versus corresponding once-daily EPL dose.
‡$P \leq 0.05$ versus ACE inhibitor or ARB plus placebo.
§$P < 0.001$ versus placebo.
‖$P < 0.001$ versus LOS.
¶$P = 0.001$ versus LOS.
#$P = 0.001$ versus placebo.
**$P \leq 0.01$ versus placebo.

Left Ventricular Dysfunction

EPHESUS (Eplerenone Post–Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) was a double-blind, placebo-controlled study that evaluated the effect of eplerenone on morbidity and mortality among patients with acute myocardial infarction (AMI) complicated by left ventricular dysfunction and heart failure (table 5).[12]

EPHESUS included 6632 patients after AMI with an ejection fraction (EF) < 40% and signs of heart failure or diabetes mellitus. Patients with diabetes could be enrolled solely on the basis of EF. Three to 14 days after the diagnosis of AMI, patients were randomized to receive eplerenone 25mg PO once daily or placebo. Patients were receiving optimal medical therapy at the time of randomization (88% aspirin, 87% ACE inhibitors or ARBs, 75% beta-blockers, 60% diuretics, 47% statins). The majority of patients were white (90%) and male (71%). Their mean EF was 33%, mean serum creatinine concentration 1.1mg/dL, and mean creatinine clearance 78mL/min. During a mean follow-up period of 16 months, 14.4% of eplerenone recipients died, compared with 16.7% of the placebo group (relative risk, 0.85; $P = 0.008$). The composite end point of hospitalization or death from CV causes occurred in 26.7% of eplerenone recipients and 30% of placebo recipients (relative risk, 0.87; $P = 0.002$). Serious hyperkalemia, defined as a serum potassium concentration $\geq$ 6mEq/L, occurred in 5.5% of eplerenone recipients, compared with 3.9% of placebo recipients ($P = 0.002$). Occurrence of hyperkalemia was associated with renal insufficiency. In patients with a creatinine clearance <50mL/min, the incidence of serious hyperkalemia was 10.1% in the combined eplerenone groups and 5.9% in the placebo group ($P = 0.006$).[12]

EPHESUS demonstrated a benefit with the addition of an aldosterone-receptor antagonist to the drug regimen of patients with LV dysfunction who were already receiving optimal medical therapy. Statistically significant reductions in hospitalizations and mortality were reported. Table 6 provides a summary of the EPHESUS study.[12]

Table 6. Effects of eplerenone (EPL) in patients with left ventricular (LV) dysfunction after acute myocardial infarction (AMI).[12]

Patient Characteristics	Study Design	Results
n = 6632; AMI (3-14 d after event) with LV dysfunction (EF $\leq$ 40%) and signs of heart failure or diabetes mellitus, patients were excluded if had serum creatinine > 2.5mg/dl and/or serum potassium > 5mmol/L.	M, R, DB, PC; therapy initiated EPL 25mg QD or placebo in addition to other therapy (88% aspirin, 86% ACE inhibitor or angiotensin-receptor blocker, 75% beta blocker, 60% diuretics, 47% statins); EPL titrated to 50mg QD	Death from any cause (%) EPL: 14.4* Placebo: 16.7 (relative risk, 0.85; $P = 0.008$) Death from CV cause/hospitalization for CV event (%) EPL: 26.7† Placebo: 30 (relative risk, 0.87;$P = 0.002$)

EF = ejection fraction; M = multicenter; R = randomized; DB = double-blind; PC = placebo-controlled; ACE = angiotensin-converting enzyme; ARBs = angiotensin-receptor blockers; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; CV = cardiovascular.

*$P = 0.008$.

†$P = 0.002$.

Additional Evidence

Dose Simplification: Not Applicable. Both agents are administered once or twice daily.

Stable Therapy: No peer reviewed data on changing from spironolactone to eplerenone or from eplerenone to spironolactone was found in a literature search of Medline/Pubmed or Ovid. The manufacturer of eplerenone reports no studies have evaluated dosing when patients are switched between the two drugs (spironolactone and eplerenone) and any patient started newly on eplerenone should be considered a new treatment with dosing as indicated for initiation of therapy in the product labeling information.

Impact on Physician Visits: No additional peer reviewed data was found on eplerenone and impact on physician visits in a literature search of Medline/Pubmed or Ovid. The manufacturer of eplerenone confirms no pharmacoeconomic or other specific studies have evaluated impact of the drug on physician visits.

IX. Conclusions

Eplerenone is the first selective aldosterone inhibitor with selective binding to mineralocorticoid receptors relative to its binding to glucocorticoid, progesterone and androgen receptors. Its efficacy as monotherapy or add-on therapy in the treatment of hypertension has been demonstrated in clinical studies. In EPHESUS, eplerenone produced statistically significant reductions in hospitalizations and mortality in patients with LV dysfunction who were already receiving optimal medical therapy. With the exception of hyperkalemia, the adverse effect profile of eplerenone either as monotherapy or in combination with other antihypertensive medications was not significantly different from that of placebo. Because of its selective binding, eplerenone may be associated with fewer progestogenic and antiandrogenic adverse effects than spironolactone including gynecomastia, impotence, and menstrual irregularities. However, results of clinical studies do not suggest that eplerenone be used preferentially before treatment with spironolactone has been tried. Additionally, hyperkalemia may be just as likely to occur with eplerenone therapy as it is with spironolactone therapy.

Therefore, eplerenone (Inspra®) is comparable to the other brands in this class and to the generics and OTC products in this class and offers no significant clinical advantage over other alternatives in general use.

X. Recommendations

No brand of eplerenone is recommended for preferred status.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Pharmacotherapy Review
Crestor (Rosuvastatin) – HMG CoA Reductase Inhibitor
AHFS Class 240608
August 11, 2004

I. Overview

Rosuvastatin is a synthetic lipid-lowering agent and belongs to the class of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors or "statins." This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.[1]

Rosuvastatin 10mg has demonstrated greater LDL lowering efficacy compared with milligram-equivalent or higher doses of some other statins. The Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) trial compared dose related effects of statins on lipid goal achievement in patients with hypercholesterolemia. Trial results demonstrated greater efficacy with rosuvastatin 10 to 40mg than atorvastatin 10 to 80mg, simvastatin 10 to 80mg, and pravastatin 10 to 40mg for achievement of the National Cholesterol Education Program Adult Treatment Panel III (ATP III) LDL-C and non-HDL-C goals.[2] Additionally, the STELLAR trial results demonstrated higher mean percent changes in high-density lipoprotein cholesterol in the rosuvastatin groups of +7.7% to +9.6% compared with +2.1% to +6.8% in all other groups.

Rosuvastatin is currently available as the brand product Crestor® and is available as 5mg, 10mg, 20mg and 40mg tablets. This review encompasses all dosage forms and strengths of the new drug. The HMG CoA Reductase Inhibitors were originally reviewed in December 2003; the previous HMG CoA Reductase Inhibitor pharmacotherapy review in full is available for reference in Appendix 1.

II. Current Treatment Guidelines

According to the ATP III guidelines, therapy with lipid-altering agents is one of several components of multiple-risk-factor intervention in individuals at increased risk for coronary heart disease due to hypercholesterolemia. Therapeutic lifestyle changes (TLC) and drug therapy are the two major treatment modalities. The TLC Diet stresses reductions in saturated fat and cholesterol intake. The following table defines LDL-C goals and cutpoints for initiation of TLC and for drug consideration.

Table 1. LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories[3]

Risk Category	LDL goal (mg/dL)	LDL level at which to initiate TLC (mg/dL)	LDL level at which to consider drug therapy (mg/dL)
CHD or CHD Risk Equivalents* (10-year risk > 20%)	< 100	≥ 100	≥ 130 (100-129: drug therapy optional)
2+ Risk Factors (10-year risk ≤ 20%)	< 130	≥ 130	10-year risk 10-20%: ≥ 130 10-year risk < 10%: ≥ 160
0 – 1 Risk Factor	< 160	≥ 160	≥ 190 (160-189: drug therapy optional)

*CHD risk equivalents include peripheral artery disease, abdominal aortic aneurysm and symptomatic carotid artery disease, diabetes, an ATP III Framingham based CHD (10-year risk assessment greater than > 20%). Diabetes qualifies as a CHD risk equivalent because it confers a high risk of new CHD within 10 years.

Updated Cholesterol Guidelines: July 13, 2004

Updated cholesterol management guidelines to the National Cholesterol Education Program's (NCEP) recommendations were issued July 13, 2004.[4, 5] The guidelines advise physicians to consider new, more intensive treatment options for people at high and moderately high risk for a heat attack. The new guidelines are endorsed by the National Heart, Lung, and Blood Institute (NHLBI), the American College of Cardiology, and the American Heart Association.

Major recommendations in the update include:

- OVERVIEW: For high-risk patients, the overall goal remains an LDL level of less than 100mg/dL. For patients at very high risk (a subset of the high-risk category), the new guidelines offer a new therapeutic option of treating to under 70mg/dl. For very high-risk patients whose LDL levels are already below 100mg/dl, there is an option to use drug therapy to reach the less than 70mg/dL goal.

CLASSIFICATION OF PATIENTS:

- **Lower/moderate risk** patients are those with 2 or more risk factors plus an under 10% risk of a heart attack in 10 years or those with 0 to 1 risk factor.
- **Moderately high risk** patients are those who have multiple (2 or more) risk factors for coronary heart disease together with a 10 to 20% risk of heart attack within 10 years.
- **High risk patients** are those who have coronary heart disease or disease of the blood vessels to the brain or extremities, or diabetes, or multiple (2 or more) risk factors (e.g. smoking, hypertension) that give them a greater than 20% chance of having a heart attack within 10 years.
- **Very high-risk** patients are those who have cardiovascular disease together with either multiple risk factors (especially diabetes), or severe and poorly controlled risk factors or metabolic syndrome. Patients hospitalized for acute coronary syndromes such as heart attack are also at very high risk.

NEW GOALS:

- For high-risk patients, the update lowers the threshold for drug therapy to an LDL of 100mg/dL or higher and recommends drug therapy for those high-risk patients whose LDL is 100 to 129mg/dL. In contrast, ATP III set the threshold for drug therapy for high-risk patients at an LDL of 130mg/dL, and made drug treatment optional for LDL 100 to 129mg/dL.
- For moderately high risk patients, the goal remains an LDL under 130mg/dL, but the update provides a therapeutic option to set a lower LDL goal of under 100mg/dL and to use drug therapy at LDL levels of 100-129mg/dL to reach this lower goal.
- The update does not revise recommendations for lower risk persons.
- The new update advises that the intensity of LDL-lowering drug therapy be sufficient to achieve at least a 30-40% reduction in LDL levels, through statins or combination therapy.

III. Indications[1]

1. Primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb) - As an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C.
2. Elevated serum TG levels (Fredrickson Type IV) - As an adjunct to diet for the treatment of patients.
3. Homozygous familial hypercholesterolemia - To reduce LDL-C, total-C, and ApoB as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

IV. Pharmacokinetics

Table 2. Pharmacokinetic Parameters of Rosuvastatin

t_{max} (hr)	3-5
Absolute Bioavailability	20%
Food Effect	• Rate of absorption decreased by 20% • Extent of absorption – no effect
Protein Binding	• 88%
Metabolism	• Approximately 10% metabolized principally by cytochrome P450 2C9
Elimination	• Elimination half-life is approximately 19 hours • Primarily excreted in feces (90%)

Pharmacokinetic studies show an approximate 2-fold elevation in median exposure in Japanese and Chinese subjects compared with Caucasians. While the mechanism is unknown, rosuvastatin appears to be more bioavailable in these patients. These increases should be considered when making rosuvastatin dosing decisions for patients of Japanese and Chinese ancestry.[1]

V. Drug Interactions

Table 3. Clinically Significant Drug Interactions[1]

Drug	Interaction	Management
Cyclosporine	When rosuvastatin 10mg was given with cyclosporine in cardiac transplant patients, rosuvastatin mean Cmax and mean AUC increased 11-fold and 7-fold, respectively, compared with healthy volunteers.	• These increases are considered to be clinically significant. • In patients taking cyclosporine, rosuvastatin therapy should be limited to 5mg once daily.
Warfarin	Coadministration of rosuvastatin to patients on stable warfarin therapy resulted in clinically significant rises in INR (>4, baseline 2-3).	• In patients taking coumarin anticoagulants and rosuvastatin concomitantly, INR should be determined before starting rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs. • Once a stable INR time has been documented, INR can be monitored at the usual intervals. • If the dose of rosuvastatin is changed, the same procedure should be repeated. • Rosuvastatin therapy has not been associated with bleeding or with changes in INR in patients not taking anticoagulants.
Gemfibrozil	Coadministration of a single rosuvastatin dose to healthy volunteers on gemfibrozil (600 mg twice daily) resulted in 2.2- and 1.9-fold, respectively, increase in mean Cmax and mean AUC of rosuvastatin.	• In patients taking gemfibrozil, rosuvastatin therapy should be limited to 5mg once daily.

VI. Adverse Drug Events

FDA approval of rosuvastatin (Crestor) was originally delayed due to safety concerns in patients taking 80mg daily doses of the drug. The concerns in clinical trials included reports of kidney damage and rhabdomyolysis. Since its approval, rosuvastatin has been linked to cases of rhabdomyolysis, renal failure, and one death.[6, 7, 8] Canada and the United Kingdom have reported seven additional cases of rhabdomyolysis and nine additional cases of kidney damage or failure.[7]

Other literature documents that adverse effects with rosuvastatin have been similar to those with other statins.[2] In clinical studies of 10,275 patients, 3.7% were discontinued due to adverse experiences attributable to rosuvastatin. The most frequent adverse events thought to be related to rosuvastatin were myalgia, constipation, asthenia, abdominal pain, and nausea.[1]

The following table lists adverse events, regardless of causality assessment, reported in ≥2% of patients in placebo-controlled clinical studies of rosuvastatin. Discontinuations due to adverse events in these studies of up to 12 weeks duration occurred in 3% of patients on rosuvastatin and 5% on placebo.[1]

Table 4. Clinical Adverse Experiences[1]

Adverse Event	Rosuvastatin n=744	Placebo n=382
Pharyngitis	9.0	7.6
Headache	5.5	5.0
Diarrhea	3.4	2.9
Dyspepsia	3.4	3.1
Nausea	3.4	3.1
Myalgia	2.8	1.3
Asthenia	2.7	2.6
Back pain	2.6	2.4
Flu syndrome	2.3	1.8
Urinary tract infection	2.3	1.6
Rhinitis	2.2	2.1
Sinusitis	2.0	1.8

Additionally, the following adverse events were reported, regardless of causality assessment, in ≥1% of 10,275 patients treated with rosuvastatin in clinical studies. The events in italics occurred in ≥2% of these patients.[1]

Table 5. Adverse Events, Regardless of Causality Assessment, in ≥1% of 10,275 Patients (n = 10,275) Events in italics occurred in ≥2% of these patients.[1]

Body System	Adverse Event (s)
Body as a Whole	Abdominal pain, accidental injury, chest pain, infection, pain, pelvic pain, and neck pain.
Cardiovascular System	Hypertension, angina pectoris, vasodilatation, and palpitation.
Digestive System	Constipation, gastroenteritis, vomiting, flatulence, periodontal abscess, and gastritis.
Endocrine	Diabetes mellitus
Hemic and Lymphatic System	Anemia and ecchymosis
Metabolic and Nutritional Disorders	Peripheral edema
Musculoskeletal System	Arthritis, arthralgia, and pathological fracture.
Nervous System	Dizziness, insomnia, hypertonia, paresthesia, depression, anxiety, vertigo and neuralgia.

Myopathy/Rhabdomyolysis[1]

- Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin and with other drugs in this class.
- Uncomplicated myalgia has been reported in rosuvastatin-treated patients.
- Creatine kinase (CK) elevations (>10 times upper limit of normal) occurred in 0.2% to 0.4% of patients taking rosuvastatin at doses up to 40mg in clinical studies.
- Treatment-related myopathy, defined as muscle aches or muscle weakness in conjunction with increases in CK values >10 times upper limit of normal, was reported in up to 0.1% of patients taking rosuvastatin doses of up to 40mg in clinical studies.
- Rare cases of rhabdomyolysis were seen with higher than recommended doses (80mg) of rosuvastatin in clinical trials.
- Factors that may predispose patients to myopathy with HMG-CoA reductase inhibitors include:
    - Advanced age (≥65 years), hypothyroidism, and renal insufficiency.
    - Doses of rosuvastatin above the recommended dosage range.

FDA Public Health Advisory June 9, 2004

In response to package labeling revisions for rosuvastatin in the European Union, the FDA issued a public health advisory for rosuvastatin in the United States.[9] At this time, there is not a black box warning in the U.S. rosuvastatin labeling, only a specific warning pertaining to liver enzymes and myopathy. The warning cautions the use of rosuvastatin in certain high risk patients with predisposing factors for myopathy, such as, renal impairment, advanced age, and hypothyroidism.

Labeling changes in European countries were a result of postmarketing adverse event reports in patients receiving the drug and highlight patient populations at increased risk for serious muscle toxicity, especially at the highest approved dose of 40mg.

In the United States, physicians are being warned to follow all recommendations for starting doses, dose adjustments, and maximum daily doses, to minimize risk of myopathy. Use of the drug is being cautioned as well in individuals identified as being at high risk for developing myopathy. Additionally, certain subgroups of patients (Japanese and patients concomitantly using cyclosporine and gemfibrozil) at greater risk of myopathy are limited to an initial starting dose of 5mg once daily and a maintenance dose not to exceed 10mg (in patients with renal failure or who are taking gemfibrozil).

The FDA is evaluating reports of adverse muscle effects with rosuvastatin, with regard to clinical severity and relationship to the drug. The frequency of reporting of muscle injury with rosuvastatin is being compared to that with other statins. Pending this evaluation, the FDA has not proposed to change the U.S. labeling for Crestor but wants to stress to physicians the importance of following current labeling recommendations.

An Update on Premarketing and Postmarking Rosuvastatin Safety

Briefing documents with unpublished reviews of safety and efficacy data from clinical trials are now available to the public on the internet before FDA advisory meetings focused on approval of new drugs. The following is a summary of this information, as reported in a correspondence published in The Lancet, by Dr. Sidney Wolfe.[10]

Preapproval

- Preapproval documents for rosuvastatin stated, "The data…show, for the first time, the development of severe myopathy and rhabdomyolysis in clinical trials submitted for the original approval of a new statin. This risk is clearly increased at the highest dose studied (80mg), which has subsequently been discontinued from development. While the risks of myopathy at lower doses appear comparable to other marketed statins, these risks may increase in special populations in which patients are exposed to higher levels of drug (drug-drug interactions, renal impairment, Japanese descent)."
- Preapproval documents also indicated, "80mg of rosuvastatin has a high frequency of creatine kinase elevations (CK>10xULN=1.9%), between what was seen in clinical trials for cerivastatin doses of 0.4mg (1.6%) and 0.8mg (2.1%) and higher than seen for all other currently approved statins."
- There was also "a higher incidence of myopathy (1%) and rhabdomyolysis (0.4%) observed in clinical trials with 80mg of rosuvastatin than reported in the original NDA or current labels for any of the currently approved statins."
- Finally, preapproval documents indicated, "...rosuvastatin was also associated with renal findings not previously reported with other statins. A small percentage of patients exposed primarily to the 80mg dose of rosuvastatin had an increased frequency of persistent proteinuria and hematuria, which in some patients was also associated with an increase in serum creatinine."
- "Out of all the patients enrolled in these trials, only 3% had an increase in serum creatinine of 30% over baseline… However, in the subgroup of patients with dipstick-positive urine (≥++ protein and ≥ + blood), the percentage of patients with an increase of serum creatinine of 30% over baseline was 14%, 16%, 24%, 33%, and 41% for 5mg, 10mg, 20mg, 40mg, and 80mg of rosuvastatin, respectively… These data suggest that some patients with greater levels of proteinuria and hematuria may progress to clinically relevant renal disease. ..this may represent an unacceptable risk since currently approved statins do not have similar renal effects..

- Rosuvastatin was approved under the belief that doses lower than 80mg would be much safer.

Postapproval

- Since marketing began, there have been 18 additional cases of rhabdomyolysis, including 11 in the U.S (over a 7 month period).
- Two of the 18 patients were taking 40mg of rosuvastatin, five were using 20mg, and 11 were using 10mg doses.
- An FDA analysis of rhabdomyolysis in currently marketed statins found that the rate of reports per million U.S. prescriptions ranged from none for fluvastatin to 1.2 per million for lovastatin, the next highest being 0.8 for simvastatin, then 0.3 for atorvastatin.
- If a majority of the 11 U.S. postmarketing reports of rhabdomyolysis meet the case definition (creatine phosphokinase conc. ≥ 10,000IU/L), as did 62% of the 8 premarketing cases, and using the FDA estimate of one million prescriptions for rosuvastatin, the rate of rhabdomyolysis reports for rosuvastatin is higher than the highest of any other currently marketed statin.
- Since marketing of rosuvastatin, there have also been eight reported cases of acute renal failure and four of renal insufficiency. Out of these cases, 9 patients were using a 10mg dose, while the others were using 40 and 80mg.
- As indicated in the correspondence and as documented by an FDA statistical review, rosuvastatin achieves only a 4% more mean LDL-lowering than comparable doses of atorvastatin. Additionally, compared with higher doses of another statin, there is no significant difference in the percentage LDL change from baseline between 5, 10, or 20mg of rosuvastatin and comparable doses of atorvastatin (20, 40, or 80mg, respectively).[11]

VII. Dosing and Administration

A standard cholesterol-lowering diet should be initiated before receiving rosuvastatin and this diet should continue during treatment. Rosuvastatin can be administered as a single dose at any time of day, with or without food.

Table 6. Indications and Dosing

	Indications	Dosage Range	Available strengths
Rosuvastatin (Crestor)	• **Hypercholesterolemia (heterozygous familial and nonfamilial)** • Mixed dyslipidemia (Fredrickson type IIa and IIb) • Homozygous FH	5 – 40mg once daily*	5mg, 10mg, 20mg, 40mg tablet

*The usual recommended starting dose of rosuvastatin (Crestor®) is 10mg once daily.

- Initiation of therapy with 5mg once daily may be considered for patients requiring less aggressive LDL-C reductions or who have predisposing factors for myopathy.
- For patients with marked hypercholesterolemia (LDL-C > 190mg/dL) and aggressive lipid targets, a 20mg starting dose may be considered.
- The 40mg dose of rosuvastatin should be reserved for those patients who have not achieved goal LDL-C at 20mg.
- After initiation and/or upon titration of rosuvastatin, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly.

Homozygous Familial Hypercholesterolemia

The recommended starting dose of rosuvastatin is 20mg once daily in patients with homozygous FH. The maximum recommended daily dose is 40mg. Rosuvastatin should be used in these patients as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable. Response to therapy should be estimated from pre-apheresis LDL-C levels.[1]

Dosage in Patients Taking Cyclosporine

In patients taking cyclosporine, therapy should be limited to rosuvastatin 5mg once daily.[1]

Concomitant Lipid-Lowering Therapy
The effect of rosuvastatin on LDL-C and total-C may be enhanced when used in combination with a bile acid binding resin. If used in combination with gemfibrozil, the dose of rosuvastatin should be limited to 10mg once daily.[1]

Dosage in Patients With Renal Insufficiency
No modification of dosage is necessary for patients with mild to moderate renal insufficiency. For patients with severe renal impairment (CrCl <30mL/min/1.73 m2) not on hemodialysis, dosing of rosuvastatin should be started at 5mg once daily and not to exceed 10mg once daily.

Special Dosing Considerations

- Rosuvastatin is contraindicated in patients with active liver disease or with unexplained persistent elevations in serum transaminases.
- Pregnancy category X. Use of HMG CoA reductase inhibitors, including rosuvastatin during pregnancy and nursing is contraindicated.
- Treatment with rosuvastatin in children has been limited to 8 patients with homozygous FH. None of the patients were below age 8.
- Per AstraZeneca, no studies have been performed to evaluate splitting or crushing of rosuvastatin. The tablets are immediate-release but are not scored.

VIII. Effectiveness

Primary Hypercholesterolemia
The Statin Therapies for Elevated Lipid Levels compared Across doses to Rosuvastatin (STELLAR) was a randomized, open-label 6-week trial in 2,431 patients with LDL cholesterol 160-250mg/dL and triglycerides ≤400mg/dL. This trial compared dose related effects of statins on lipid goal achievement in patients with hypercholesterolemia. Trial results indicate that rosuvastatin 10 to 40mg has greater efficacy than atorvastatin 10 to 80mg, simvastatin 10 to 80mg, and pravastatin 10 to 40mg for achievement of the National Cholesterol Education Program Adult Treatment Panel III (ATP III) LDL-C and non-HDL-C goals.[2]

Table 7. Percent Change in LDL-C From Baseline to Week 6 by Treatment Group (sample sizes ranging from 156-167 patients per group)

	Treatment Daily Dose			
Treatment	**10mg**	**20mg**	**40mg**	**80mg**
Rosuvastatin	-46*	-52†	-55‡	---
Atorvastatin	-37	-43	-48	-51
Pravastatin	-20	-24	-30	---
Simvastatin	-28	-35	-39	-46

*Rosuvastatin 10mg reduced LDL-C significantly more than atorvastatin 10mg; pravastatin 10mg, 20mg, and 40mg; simvastatin 10mg, 20mg, and 40mg. (p<0.002).
†Rosuvastatin 20mg reduced LDL-C significantly more than atorvastatin 20mg and 40mg; pravastatin 20mg, and 40mg; simvastatin 20mg, 40mg, and 80mg. (p<0.002).
‡Rosuvastatin 40mg reduced LDL-C significantly more than atorvastatin 40mg; pravastatin 40mg; simvastatin 40mg, and 80mg (p<0.002).
§ Corresponding standard errors are approximately 1.00

Additionally rosuvastatin 10-40mg increased HDL cholesterol by 7.7-9.6%, compared to 2.1-5.7% with atorvastatin 10-80mg, 5.2-6.8% with simvastatin 10-80mg, and 3.2-5.6% with pravastatin 10-40mg.

Table 8. Mean % Change in HDL from Baseline at Week 6

	Rosuvastatin: 10-40mg	Atorvastatin: 10-80mg	Simvastatin: 10-80mg	Pravastatin: 10-40mg
Mean % Change in HDL from Baseline	7.7-9.6	2.1-5.7	5.2-6.8	3.2-5.6

Across dose ranges, rosuvastatin reduced total cholesterol significantly more (p <0.001) than all comparators and triglycerides significantly more (p <0.001) than simvastatin and pravastatin.

Hypertriglyceridemia

As demonstrated in the STELLAR trial, rosuvastatin reduced triglycerides to a significantly greater extent that simvastatin and pravastatin. In a pooled analysis of 5 randomized double-blind trials, rosuvastatin 10mg daily lowered triglycerides as effectively as atorvastatin 10mg (19.2% vs. 17.6%) and more effectively than 20mg of simvastatin or pravastatin (20.2% vs. 12.2% and 12.4%, $p < 0.01$).[12]

Table 9. Mean Percent Change in Triglycerides from Baseline at 12 weeks: Rosuvastatin 10mg vs. Atorvastatin 10mg[12]

	Rosuvastatin 10mg	Atorvastatin 10mg
Mean % Change in Triglycerides	-19.2	-17.6

Table 10. Mean Percent Change in Triglycerides from Baseline at 12 weeks: Rosuvastatin 10mg vs. Simvastatin 20mg and Pravastatin 20mg[12]

	Rosuvastatin 10mg	Simvastatin 20mg	Pravastatin 20mg
Mean % Change in Triglycerides	- 20.2*	-12.2	-12.4

*$P < 0.01$ vs. simvastatin and pravastatin

Combination Therapy

An open-label, 24-week trial in 270 patients with hypertriglyceridemia and low HDL cholesterol (≤45mg/dL) found that rosuvastatin 10mg plus extended-release niacin 2 g increased HDL cholesterol 24%, compared to 11% with rosuvastatin 40mg alone, 12% with niacin 2g alone, and 17% with rosuvastatin 40mg and extended-release niacin 1g. Rosuvastatin 10mg plus niacin 2g had less effect on LDL cholesterol than rosuvastatin 40mg alone (-36% vs. -48%).[13]

Table 11. Percent Change in HDL and LDL from Baseline at Week 24[13]

	Rosuvastatin 10mg + Niacin Extended Release 2g	Rosuvastatin 40mg	Niacin 2g
HDL	24*	11	12
LDL	-36	-48†	

* $p < 0.001$ (versus rosuvastatin 40mg)

† $p < 0.01$

Switching from Other Statin Therapy to Rosuvastatin

In a multinational trial of 3,140 patients with hypercholesterolemia and coronary heart disease, atherosclerosis, or type 2 diabetes, patients were randomized to rosuvastatin 10mg, atorvastatin 10 or 20mg, simvastatin 20mg, or pravastatin 40mg for 8 weeks.[14] Patients either remained on these treatments for another 8 weeks or were switched to rosuvastatin 10-20mg. Significant improvement in LDL-C goal achievement was found for patients who switched to rosuvastatin 10mg, compared to patients who remained on atorvastatin 10mg (86% vs. 80%, P<0.05), simvastatin 20mg (86% vs. 72%, P<0.0001), and pravastatin 40mg (88% vs. 66%, P<0.0001), and between patients switched to rosuvastatin 20mg and those who remained on atorvastatin 20mg (90% vs. 84%, P<0.01).

Additional Evidence

Dose Simplification: Not Applicable. The HMG-Co-A Reductase inhibitors are all routinely dosed once daily.

Stable Therapy: One previously mentioned study documented benefits in patients switched from certain doses of atorvastatin, simvastatin, and pravastatin, to rosuvastatin.[14] Another report in the literature has documented an effective therapeutic–interchange clinic at a military medical center as a means of monitoring outcomes with statin therapy and individualizing patient care.[15]
In evaluating the effects of comorbidities and patient characteristics on treatment continuation among patients starting their first course of lipid-lowering drug therapy, 22,408 patients within the UK General Practice Research Database were identified.[16] Discontinuation and switching of lipid-lowering therapy was common during the study period. More frequent physician visits, more concurrent cardiovascular medications, diabetes, and fewer noncardiovascular medications were associated with treatment continuation of lipid-lowering drugs. Among patients who switched therapy, prescribing of a statin as the substituted lipid-lowering drug, more concurrent cardiovascular medications, and later treatment switching were related to a higher probability of treatment continuation after switching lipid lowering drugs. This suggests treatment continuation after initiation or switching of lipid-lowering therapy largely increases with concomitant cardiovascular comorbidities, and more healthcare utilization, and is more common for statins than for other lipid-lowering therapies.

Impact on Physician Visits: Most patients started on statin therapy in clinical practice are maintained on their starting dose, and this frequently results in inadequate control of cholesterol. A number of factors limit dose titration in practice, including safety of prescribing statins at high doses and the additional office visits required for evaluations and monitoring.[17] For these reasons, choice of statin appears to be one of the important factors influencing the success of therapy.
One study looked at the total resources required for care to reach NCEP goals with various statin drugs (atorvastatin, simvastatin, lovastatin, and fluvastatin).[18] Because the focus of this review is on rosuvastatin and it was not included in the previously mentioned study, the results of this study will be included in the future re-review of the HMGCo-A Reductase Inhibitor class (AHFS 240608).

IX. Conclusions

Recommended doses of rosuvastatin have demonstrated decreases in LDL cholesterol and triglycerides more than recommended doses of atorvastatin, and more than other statins. Additionally, rosuvastatin appears to increase HDL cholesterol slightly more than other statins. However, larger doses of other statins produce similar reductions in all cholesterol parameters. Reports of higher serum concentrations in Asians are a concern because of increased risk of myopathy. Concern over the safety of rosuvastatin with the issuance of the FDA Public Health Advisory, and pending evaluation of all rosuvastatin safety data by the FDA, makes statins with a longer safety record more favorable. Should the FDA find that rosuvastatin has a higher risk for adverse events as compared to currently available statins, it is possible the drug will be withdrawn from the market.

Until rosuvastatin's safety can be established, rosuvastatin should be reserved for, and used with caution in, only those patients who have not responded adequately to statins with a longer safety record. The treatment of hyperlipidemia in this population should be considered unique and not within the scope of the general use of the drugs within this class.

Therefore, rosuvastatin is comparable to the other brands in this class and to the generics and OTC products in this class and offers no significant advantage over other alternatives in general use.

X. Recommendations

No brand of rosuvastatin is recommended for preferred status.

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Alabama Medicaid Agency
Antidepressant Warning from the Food and Drug Administration
An Update
August 11, 2004

Background

Prevalence estimates indicate that up to 6% of adolescents currently meet the criteria for major depressive disorder and up to 25% have been affected by this disorder by their late teens.[1] Depression is a major risk factor for suicide, which ranks third as a cause of death among teens in the United States. In fact, increased use of antidepressants among children 10-19 years of age has been accompanied by a significant decrease in the suicide rate in this age group. For each 1% increase in the use of SSRIs among adolescents, there was a decrease of 0.23 suicides per 100,000 adolescents per year.

Since June 2003, the Food and Drug Administration (FDA) has been reviewing results of 25 trials of antidepressant studies in children. This investigation began after initial reports on studies with Paxil, and subsequent reports on other antidepressants, that the drugs appeared to increase the risk of suicidal thoughts and actions in children in the studies. However, no suicides were reported in any of the trials. On close examination of initial reports, it was unclear whether certain behaviors reported in the studies were actual suicide attempts, or other self-injurious behaviors that were not suicide related.[2]

This investigation has been complicated by the lack of standardized terminology for suicidal acts among the studies being reviewed. There may have been adverse events classified as suicidal, while other suicidal adverse events may have been missed. For example, one case classified as a suicide attempt in which a child slapped herself in the head, and another case in which a child stabbed himself in the neck with a pencil, that was classified as an accidental injury.[2] As a result, the FDA has established an independent panel of internationally-recognized experts in suicide assessment and adolescent suicide research, to classify the data consistently across trials, and to establish a common set of guidelines, in order to interpret adverse events reported from the pediatric depression trials. The results of this project are expected by end of the summer 2004.

The Update: Important Questions Answered

What Has The FDA Announced Regarding The Use Of Antidepressants?
On March 22, 2004 the FDA issued a Public Health Advisory, asking the manufacturers of 10 antidepressant drugs to strengthen the "warnings" section of their package insert to encourage close observation for worsening depression or the emergence of suicidal thinking and behavior in both adult and pediatric patients being treated with these agents, particularly for depression but also for other psychiatric and non psychiatric disorders.[3, 4] Discontinuation of medication may be appropriate in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of he patient's presenting symptoms. Prescribers, patients, and their caregivers should be alert to the emergence of the following symptoms: anxiety, agitation, panic attacks, insomnia, irritability, hostility, impulsivity, akathisia (severe restlessness), hypomania, and mania. Although a causal link has not been established between these symptoms and worsening of depression or the emergence of suicidal impulses, medications may need to be discontinued when symptoms are severe, abrupt in onset, or were not a part of the patient's presenting symptoms.

What Drugs Are Involved In The Announced Label Change?
Prozac (fluoxetine), Zoloft (sertraline), Paxil (paroxetine), Luvox (fluvoxamine), Celexa (citalopram), Lexapro (escitalopram), Wellbutrin (bupropion), Effexor (venlafaxine), Serzone (nefazodone), and Remeron (mirtazapine)[4, 5]

Why Is The Warning Being Made Prior To The Completion Of The FDA's Analysis Of Controlled Trials?
The Psychopharmacological Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-infective Drugs Advisory Committee recommended it would be useful to strengthen the labeling for these antidepressant products by drawing more attention to the need for close monitoring of patients (adults, children and adolescents) being treated with antidepressants.

When Will The FDA's Review Of Data From The Trials Be Completed?
The FDA plans to hold a public meeting later this summer to update the Psychopharmacological Drugs Advisory Committee and the Pediatric Subcommittee of the Anti-infective Drugs Advisory Committee of the results of the re-analysis of the pediatric suicidality data to seek their expert input.

Conclusion

At this time, it is important that prescribers, patients, and caregivers are aware of the strengthened warning in the labeling of the ten antidepressant medications listed above. Patients are encouraged to consult their physician to discuss the best course of action when worsening symptoms of depression are observed, with the emergence of suicidal thinking, or due to other symptoms mentioned in box 1 above. Antidepressant medications should not be stopped abruptly, as discontinuation symptoms may occur.

It is also important to remember that Prozac (fluoxetine) is the only FDA approved drug for use in children and adolescents for the treatment of major depressive disorder. Prozac (fluoxetine), Zoloft (sertraline), and Luvox (fluvoxamine) are approved for use in children and adolescents for the treatment of obsessive-compulsive disorder. The other antidepressants have no approved uses in children.

Heritage Information Systems, Inc will provide necessary and important updates to Alabama Medicaid Agency as it becomes available from the FDA.

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